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Obstructive Urinary Tract Lesions in Children

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• Diseases that cause obstruction to the passage of urine in children almost always are owing to developmental defects. The most common site of obstruction in children, both male and female, is the neck of the bladder.

The importance of recognizing these conditions in the early stage of their development is emphasized by the fact that renal damage that may lead to failure occurs much more rapidly in children than in adults.

Symptoms are often insignificant. Recurrent or chronic infection in the urine should always be regarded as a warning sign. Investigation of the urinary tract in children is relatively easy, and with the improved methods of treatment now available, cure can be effected in virtually all cases in which irreversible changes in the kidneys have not occurred at the time of recognition.

OBSTRUCTIVE LESIONS of the urinary tract in children are almost entirely of congenital origin and are frequently associated with anomalies of the genital tract as well as of other unrelated parts of the body. They are located at the ureteropelvic junction, the ureterovesical junction, the neck of the bladder and the external urethral meatus. Occasionally obstruction is caused by ectopic position of a ureter.

Obstructions at the Ureteropelvic Junction

Obstructions at the ureteropelvic junction are of three general types: (1) high insertion of the ureter above the most dependent portion of the pelvis, (2) narrowing of the lumen of the pelvic outlet as a result of fibromuscular thickening of the ureteral wall in this area and (3) extrinsic bands with or without aberrant vessels impinging on the ureteropelvic junction. A mucosal valve located at the ureteropelvic junction may be added as a fourth type. Any combination of these may occur in a single case.

In most cases such lesions cause no symptoms while the child is young. As hydronephrosis develops, however, increased intrapelvic pressure causes pain, usually intermittent. Patients in whom infection develops have more symptoms and pyuria is usually persistent. The diagnosis is made by a complete study of the urinary tract. A hydronephrotic kidney can usually be palpated in a well relaxed child and palpation is perhaps more accurate if the child is lying on the abdomen. The location of the lesion is confirmed by roentgenographic study of the urinary tract. Intravenous or intramuscular urograms are diagnostic in many cases and may be supplemented by retrograde pyelo-ureterograms. Treatment is by the same kind of plastic procedures on the ureteropelvic junction as those carried out in adults, and destruction of a kidney as a result of hydronephrotic atrophy or pyonephrosis should rarely occur if the condition is recognized and treated early. The importance of early

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recognition is obvious if there is bilateral obstruction at the ureteropelvic junction or if the patient congenitally has but one kidney. It is important to determine whether or not the obstruction is bilateral, the amount of renal damage that has occurred and the presence or absence of other associated anomalies. A fused or "horseshoe" kidney is more liable to defective drainage than is a kidney that is normally situated. Hydronephrosis of clinical importance will develop in a few such cases. Surgical treatment entails division of the isthmus with lateral suspension of the lower poles of the kidneys combined with plastic reconstruction of the ureteropelvic junction or, in a few cases, removal of the hydronephrotic side.

Obstructions at Ureterovesical Junction

Obstructions at the ureterovesical junction are of two types: (1) ureterocele in which the obstruction involves only the mucosal orifice and (2) congenital narrowing of the entire intramural portion of the ureter. In the author's experience the former is chiefly unilateral and the latter bilateral. Damage to the upper urinary tract is in proportion to the degree of obstruction. Symptoms may be absent until severe hydronephrosis develops and may be initiated only by intervening infection. Ureteroceles are sometimes quite large and may obstruct the internal vesical orifice and cause acute retention of urine. In females a portion of the sac may be extruded through the external urethral orifice. The treatment of ureteroceles is simple. Opening the cyst with a cutting current and resection of the redundant mucosa is all that is necessary. In small children with large ureteroceles this is more adequately done through a suprapubic approach. Strictures involving the intramural portion of the ureter may be treated by ureteral meatotomy or by severing the ureter where it enters the posterior wall of the bladder and reimplanting it into a different position. The author's experience with ureteral meatotomy has been unsatisfactory in that in too many cases scar tissue caused new obstruction. Good results have so far been obtained from reimplanting the ureters. Reimplantation is carried out exactly as it is in adults. Children lend themselves remarkably well to the procedure and they usually are able to leave the hospital in two to three weeks.

Obstructions at the Internal Vesical Orifice

Obstructions at the internal vesical orifice in children are much more common than is generally recognized. In a few cases the obstruction is caused by a congenital prostatic valve. (The condition was noted in three of forty-five cases observed by the author in which open operation was done.) The obstruction may be caused by the valves alone or in conjunction with an enlarged verumontanum. Most obstructions at the internal vesical orifice in this age group, however, are caused by fibromuscular thickening in the area of the internal sphincter. There may be a complete contracture with involvement of only the posterior half of the neck of the bladder, simulating a prostatic bar in adult males. Obstruction of this type occurs about as often in females as in males. It is frequently associated with anomalies of the genital tract and in a surprising number of cases congenital absence of one kidney or some other associated anomaly has been observed. Not infrequently there are minimal symptoms or none at all until the upper urinary tract has become severely damaged, even to the point of irreversible renal failure. Frequency, straining, bed-wetting and overflow incontinence may occur. Any abnormal voiding pattern in a child should be promptly investigated. Infection is likely to occur and is usually persistent. Recurrent chills and fever are common. Infection added to the effects of back pressure increases the rapidity with which renal failure takes place.

Simple procedures are usually adequate to make the diagnosis. Intravenous urograms will indicate the functional value of the kidneys and usually any structural changes that have occurred unless the renal function has been severely damaged. Retrograde cystography is a most valuable procedure not only in establishing that there is obstruction at the neck of the bladder but also in indicating the amount of damage that has occurred as a result of the obstruction. One point that has probably not been emphasized as much as it should is that in many cases there is little residual urine even with a moderately dilated bladder. Recurrent or persistent pyuria is usual in such cases. A retrograde cystogram may be supplemented by cystoscopy but in most cases it is unnecessary. If the obstruction is recognized as early as it should be in the younger age group, the urethra is too small for insertion of an instrument that will provide adequate vision of the posterior urethra.

Surgical Treatment of Obstructions

Surgical procedures of two types have been used for the removal of obstruction at the neck of the bladder in children: transurethral resection and suprapubic or a modified retropubic approach. Transurethral resection has been widely used and is still a popular method in many medical centers. To the author, and perhaps to others, this procedure has not been uniformly satisfactory in small children. The urethra of a male infant will not accommodate an instrument of sufficient size to carry an adequate working element even with the aid of perineal urethrostomy. Hence, usually not

enough tissue is removed and repeated resection is necessary; and it should be emphasized that as long as any obstructive tissue remains, damage to the upper urinary tract continues and the urine if infected cannot be made sterile. Moreover, in small children transurethral instrumentation may cause urethral stricture. Transurethral resection may be quite adequate, however, for removal of obstructions in older children.

In 1948 the author started using a modified retropubic approach for removal of congenital obstructions of the neck of the bladder. In a child the neck of the bladder is higher in the pelvis than it is in an adult and is therefore easily accessible through an open approach. In the method used, the neck of the bladder is exposed through a low midline incision down to the symphysis. The bladder is opened immediately above the internal vesical orifice and the incision extended distally as far as is necessary to expose the entire posterior urethra even to the superior layer of the triangular ligament. All the obstructing tissue is easily removed by sharp dissection and the cut margins are approximated by a suture, which is usually adequate to control all bleeding. Only vessels from which blood spurts need be ligated. It is usually wise to cut completely through the wall of the bladder at this area in order to be quite certain that all obstructing tissue is removed. If the closure is adequate, there is no danger of urinary extravasation. Prostatic valves are destroyed by the high frequency current and enlargement of the verumontanum is treated in the same manner. The neck of the bladder is closed by continuous sutures and, unless the upper urinary tract has been decompensated by back pressure, drainage is accomplished by an indwelling urethral catheter, which is removed at the end of a week. If the patient has a large atonic bladder and especially if there is ureteral reflux, suprapubic drainage should be employed as long as is necessary to permit the upper urinary tract to return to normal. From six months to one year may be required. Children seem to tolerate suprapubic drainage remarkably well.

Results of Surgical Treatment

Forty-five children, 25 of them boys, were treated by this method. The only complication of importance was epididymitis which developed in one child after discharge from the hospital. The maximum duration of hospitalization was 18 days. Results were uniformly good in all 45 cases.

Pinpoint External Urethral Meatus

A pinpoint external urethral meatus is said to be one of the most frequently encountered obstructions of the lower urinary tract. However, the author has observed it less often than obstruction at the internal vesical orifice. Nevertheless, this simple obstruction can be of as much clinical importance as the latter lesion and cases have been reported in which renal failure has occurred. One of the most important features of a pinpoint meatus is recognition of its presence and the complications that can arise as a result of it. Treatment consists in meatotomy followed by passage of sounds. Since it is not unusual for a patient to have obstruction at more than one site—pinpoint meatus and obstruction of the neck of the vesicle, for instance—the urinary tract must be completely studied in all cases. Pinpoint meatus is not infrequent in females and can be quite as important as the equivalent condition in males.

Duplicated Ureters

Duplication is one of the commonest anomalies of the upper urinary tract. If the duplicate ureter opens in normal position at the lateral angle of the trigone and there is no obstruction, it is of no clinical importance. In a large proportion of cases, however, the duplicate vessel opens in an ectopic position, such as the posterior urethra, seminal vesicles, rectum, uterus, vagina, anterior urethra or Bartholin gland. In all such cases drainage is defective and there is hydronephrosis of the renal segment that is served by the ectopic ureter, most often the upper pole. If the duplicate ureter opens into the posterior urethra there may be no symptoms until, infection complicating the condition, the patient has pain in the renal area and recurrent chills and fever. Not infrequently in such circumstances chills and fever follow exercise. Usually in intravenous urograms the pelvis on the involved side appears to be normal but not in a normal relationship to the total renal shadow. In many cases the function of the involved segment of the kidney is reduced to the extent that the contrast medium will not concentrate in it, and the diagnosis then depends upon detailed search of the posterior urethra for the ectopic ureteral orifice. Frequently it can be located by injecting indigo carmine intravenously, then compressing the kidney bimanually during the search to force urine into the visual field. This method is useful, however, only if some degree of function has been maintained in the segment of kidney that drains through the ectopic orifice. Always when the orifice opens distal to the external sphincter there is constant dribbling of urine.

The history in such cases is characteristic. The child urinates at normal intervals and in normal amounts (indicating that there is a bladder and a competent external sphincter) yet is constantly wet.

The majority of patients observed by the author were girls. The ectopic orifice was more frequently seen in the posterior margin of the external urethral orifice than in any other location. Pyelo-ureterographic visualization of retrograde catheterization of the ectopic ureter will identify the kidney to which it is attached and show the amount of dilation of the ureter and the renal segment.

Treatment is surgical. In view of the fact that in duplicated pelves the upper pelvis serves only one-fourth to one-third of the total renal mass, resection of that portion can usually be accomplished with preservation of enough renal tissue on that side to support life even in the absence of the opposite kidney. In cases in which the involved segment of the kidney has maintained good function the ureter may be reimplanted into the bladder. This would be especially indicated in cases in which the lower pelvis is involved. Anastomosis to the adjoining ureter or implantation into the rectosigmoid colon is not to be considered in the management of ectopic ureters.

Dilated Tortuous Ureters

Another kind of obstruction is that which occurs from dilated tortuous ureters as a result of obstruction at some point in the lower urinary tract. After the primary obstruction is removed, dilated tortuous ureters have a tendency to return to normal length and diameter. On the other hand, if the obstruction has been complicated by infection, frequently periureteritis develops with adhesions between the loops of ureter that prevent the normal recuperative tendency.

Treatment consists in freeing the ureter, resection of the redundant portion (frequently as much as one-third to one-half of the entire length) and reanastomosis of the upper and lower segments. The urinary stream may be diverted by ureterostomy above the point of anastomosis or by nephrostomy.

Infected Urine

Infected urine is a frequent sign of an obstructive lesion in some part of the urinary tract. It is the usual practice in the majority of medical centers to make a complete study of the urinary tract after the second or third attack and such studies are mandatory in all cases of persistent pyuria. Intravenous urography in the majority of cases will supply all the information needed or it will indicate the necessity for supplementary studies. The contrast medium is tolerated almost entirely without reaction and a proportionately larger dose can be given than is ordinarily administered to adults, thus increasing the likelihood of obtaining diagnostic visualization.

A point to be borne in mind with regard to obstructions of the urinary tract is that in children there is in general good prospect for salvage. In many cases in which there seem to be irreversible changes, relatively normal function will be regained after adequate surgical treatment.

Prytania and Aline Streets.

Phenylbutazone: An Evaluation of Its Use

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• Phenylbutazone (Butazolidin®), one of the newer antirheumatic drugs, while providing varying degrees of symptomatic relief in various types of rheumatism, may also cause serious toxic side effects. It is most effective in acute gout, and slightly less so in rheumatoid arthritis, of both the spondylitic and peripheral types. Its use in degenerative arthritis is not indicated. Its toxic side effects include gastrointestinal upsets, edema, rash, stomatitis, purpura, hematuria, agranulocytosis and reactivation of peptic ulcer. Several fatalities have been reported. It is, however, a valuable drug if used properly. Extreme caution should be exercised in selection of patients, in administration of the drug and in continuous observation of patients receiving it.

A GREAT DEAL of controversy has arisen around the newest of the antirheumatic drugs, phenylbutazone (marketed under the trade name of Butazolidin®) owing principally to the fact that it causes serious toxic side effects in some patients, although in most instances these effects are minor and rapidly reversible.

Phenylbutazone is a pyrazole derivative related to aminopyrine. It was first used as a solvent for aminopyrine to permit parenteral administration of that drug. Soon it was observed that phenylbutazone has potent antirheumatic properties of its own, and it has been used by itself for the past 18 to 24 months. In laboratory studies the drug was observed to have analgesic, antihistaminic and antipyretic properties, and to decrease capillary permeability.[6, 16, 20] It is rapidly absorbed when given orally, and somewhat less so when given intramuscularly. The highest concentration in the plasma after a single dose occurs in two hours when it is given by mouth, and in six to ten hours when injected intramuscularly.[3] One third of the drug contained in the plasma is strongly bound to the plasma protein. With repeated daily dosage the amount in the plasma is remarkably constant in each patient, but the level of constancy varies considerably between patients. It ranges from 60 mg. per liter in some cases to 140 mg. in others. When that level is reached, increased dosage does not increase the amount in the plasma, the excess presumably being rapidly metabolized and excreted. It is thought that sodium retention occurs when the content of phenylbutazone in the plasma reaches 50 mg. per liter, but there is no anti-inflammatory effect until a level of 100 mg. per liter is reached. When the drug is discontinued, it takes approximately seven to ten days for total excretion of it.[2, 3, 16]

There is no doubt in the opinion of almost all observers who have written about phenylbutazone that it provides varying degrees of relief of pain in a majority of patients with rheumatic diseases, and to a lesser degree decreases swelling and increases mobility of the affected parts. The relief usually occurs within two or three days after administration is begun and the effect is completely dissipated within seven to ten days after it is discontinued. It is important to recognize that phenylbutazone, like the steroids, has no curative properties.

The most dramatic effect of the drug is in acute gout, where it promptly brings about pronounced relief in 80 to 85 per cent of cases—sometimes complete remission within 24 to 48 hours. It is reported to be of value in maintenance therapy of chronic gout, but since there are other less toxic drugs, such as colchicine and probenecid, which are relatively effective in such cases, it is not recommended for routine use.[11, 16, 19, 21] Phenylbutazone is also very effective in relief of pain in nonarticular rheumatism, such as "painful shoulder" and bursitis, but remissions may not be as complete or lasting as in gout.[25]

In rheumatoid arthritis, 50 to 80 per cent of patients get varying degrees of subjective relief of pain. The drug seems to be slightly more effective in the spondylitic than in the peripheral type of the disease. There is some disagreement as to objective relief obtained by use of phenylbutazone, but in a review of the literature it appeared that some objective improvement was noted in about 50 per cent of patients.

Phenylbutazone is also effective in the relief of symptoms in degenerative arthritis in a smaller proportion of patients, but its use in this disease is not ordinarily advised because of the age of the patients (for reasons stated below). It may be said that

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the effectiveness of phenylbutazone in the treatment of chronic rheumatic diseases is roughly inversely proportional to the duration of the disease.[12, 16, 22, 25, 27, 28, 32]

Toxic reactions occur in about 25 per cent of patients receiving phenylbutazone, but only in about 10 per cent is it necessary to discontinue administration. The common reactions are gastrointestinal upset, edema and rash. Less common is the occurrence of more generalized allergic reactions with stomatitis, purpura, hematuria and agranulocytosis. Several patients have died of agranulocytosis. Reactivation of preexisting peptic ulcer has occurred, and several cases of unexplained gastrointestinal bleeding have been reported.* Another reaction not reported, which the author has observed, is moderate to pronounced increase in blood pressure, with or without obvious edema. One investigator reported the occurrence of optic neuritis during the administration of phenylbutazone, but the status of the case is as yet not well defined.[7]

From the foregoing it is obvious that the value of phenylbutazone in the relief of symptoms of rheumatic diseases is now generally accepted, and that the drug sometimes causes undesirable and occasionally serious side effects. However, it is for use in dealing with a group of diseases which are notably difficult to control and, as yet, impossible to "cure," and for which there are relatively few effective drugs. Certainly, the incidence of toxic reactions to gold is almost as high as to phenylbutazone, and the dangers just about as great, although when gold is effective the improvement is prolonged. The use of steroids, corticotropin (ACTH) and cortisone, causes almost as many immediate side effects and no one knows what the really long term administration of them will produce. Physicians continue to use these drugs, but with great care. The author believes that the same should apply to the use of phenylbutazone; that both the good and the bad features of the drug should be recognized and constant vigil kept for the development of known and unknown side effects.

The following recommendations are offered:

Phenylbutazone is a valuable adjunct to the armamentarium available in the treatment of rheumatic diseases, but it is also a potentially dangerous drug and must be treated as such. Whether the drug should be used or not depends upon the real need for relief provided by it, balanced against the danger of possible toxic reactions. Certainly it should not be used in cases in which other less toxic drugs will provide as adequate, or nearly as adequate, relief.

Phenylbutazone should not be given to patients with a history of peptic ulcer and it should be used with great caution, if at all, in patients with a history of allergic reaction to drugs. In patients over 60 years of age and in others with known cardiac disease, or any disease complicated by edema, the intake of sodium should be restricted, if phenylbutazone is to be given at all.

Dosage of the drug should obviously be kept at a minimum;[9,13] never should it exceed 800 mg. daily.[12] It is now quite clear that larger dosage does not increase effectiveness. In some few cases, adequate relief can be obtained with doses of 100 mg. daily, or even less.

The drug should be taken with food, or with an anti-acid preparation that contains no sodium, to minimize gastric irritation. If the patient is given adequate amounts of phenylbutazone yet has no relief of symptoms within four to seven days, administration should be discontinued, for it is extremely unlikely that any improvement will occur. Patients should never be given prescriptions for large amounts of the drug, lest they neglect regular visits to the physician.[10]

The blood should be examined before administration of the drug is started, at frequent intervals during the institution of treatment, and regularly thereafter as long as therapy is continued. At each visit to the office, the physician should weigh the patient,[9] determine the blood pressure, and question him as to subjective symptoms. The author also believes that when phenylbutazone is given to a patient with a chronic rheumatic disease, he should be fully informed as to its lack of curative properties and its potential toxic effects, so that he can better cooperate with the physician.

In general, phenylbutazone should not be used by a physician who is not willing, or able, to accept the responsibility of careful continuous observation of each patient receiving the drug.

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Anoxemia and Brain Disease

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• The author advances the concept that anoxemia, either in its general or restricted form, or both, is probably responsible for a considerable portion of "degenerative diseases," whose etiologic delineation has not yet been traced. It is necessary, he believes, to enlarge greatly the comprehension of the disordered circulatory states to include oxygen want and thereby account for a number of conditions hitherto considered to be of unknown cause. More than this, he finds in oxygen want an explanation of the mechanism of a number of individual lesions or details of lesions otherwise not well understood. The author believes it is very likely that an understanding of cerebral anoxia in its ultimate ramifications will open still wider doors to the understanding of certain clinical syndromes the cause of which remains obscure.

IT HAS BECOME a fundamental doctrine in medical science that the most direct approach to a problem in prevention and treatment of a given disease is by way of knowledge of the cause. The earliest concepts regarding treatment were best crystallized with respect to traumatic lesions, for it was not difficult to reason from cause to effect in these circumstances. In the case of fractures of the skull, the first surgeons soon appreciated the necessity of elevation of depressed fragments and of providing drainage for complicating intracranial hemorrhage. It was possible to understand the significance of a simple tumor formation as a space-occupying element which made functions awkward because of its mass. But it was a long and barren era between the period of the Greek and the Roman physicians who practiced medicine at the beginning of the Christian era and the time of Pasteur and Lister, for in all that time there was no way of knowing the meaning of what came to be called "laudable pus." And the surgical arts had only half a century to learn to deal with suppurative lesions before the age of antibiotics had set in. Neurosurgeons had not yet, either collectively or individually, attained the percentage of cures achieved by Macewen, before the problem of abscess of the brain was almost completely wiped out by the introduction of penicillin. And what could now be a better answer to therapy of malignant gliomas than to know something of the basic nature and means of evolution of the lethal seeds that stimulate them to grow?

Medical students are early taught that human disorders are either congenital (or hereditary) or acquired, and that if acquired they are of traumatic, infectious, vascular, toxic, metabolic or neoplastic nature. The degenerative diseases are usually put in a special class since, by and large, they cannot readily be accounted for.

MEDICAL HISTORY AND ETIOLOGY

One need go back only a little more than a century to the time of Cruveilhier[13] (1829-42) to trace the short history of useful knowledge with respect to the causes of cerebral disease. The magnificent lithographs of meningiomas and metastatic tumors, hemorrhages and softenings, meningitis and abscess—yes, even of multiple sclerosis—as portrayed in his atlas, make it perfectly clear that the common entities of nervous disease were definitely recognized. But Cruveilhier and his contemporaries often confused primary with secondary growths, and even mistook fungus cerebri for sarcoma of the skull because all tumefactions which eroded the skull were in their day designated as "tumeurs fungueuses" in keeping with the tradition of Antoine Louis established half a century before. Granulomas were confused with true neoplasms, and infection of the middle ear was considered secondary to the abscess in the brain, thus interchanging the etiological cart and horse. But the introduction of the microscope helped solve the problem of classification of tumors, and the test tube ultimately distinguished between purulent and granulomatous lesions. The discovery of the spirochete further opened up the door to knowledge of the kaleidoscopic aspects of syphilis, and appreciation of the nature of arteriosclerosis soon brought explanation of the most common of encephalic lesions—the vascular ones.

Somewhat less conspicuous among his famous gallery of lesions were Cruveilhier's depictions of brains with partial and irregular atrophy, lesions that already had been described by his compatriot, Cazauviehl (1827).[4] With the passing decades, there

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was added, one by one, congeries of bizarre, divergent and baffling lesions which now constitute the last group of diseases of unknown or uncertain cause. These traditionally have been considered "degenerative" in nature. Among them are cerebral atrophy —generalized, hemispheral, lobar or convolutional —a smaller group of central disorders, including cystic degeneration and the demyelinizing diseases, and a still more circumscribed group of ganglionic lesions, most of which may be included under the euphonic terms *status marmoratus* and *status dysmyelinisatus*. Since these lesion-complexes (for they are by no means isolated structural entities) are now known to be intimately associated with epilepsy, cerebral palsy and mental deficiency, interest has developed anew in their genesis (Courville, 1950, 1952).[9, 10]

ETIOLOGY OF "DEGENERATIVE DISORDERS" OF THE BRAIN

Since Virchow (1867)[32] applied the term *infantile encephalitis* to one of this group (infantile cystic degeneration of the brain) some eighty-odd years ago, these various diseases have been more or less critically studied by many earnest students of cerebral disease. Different investigators have variously ascribed them to hereditary deficits, infections (encephalitis), specific or non-specific degeneration, vascular disorders, and finally birth trauma—the possibilities entertained depending upon the particular viewpoint of the investigator: whether he was most impressed by the occasional familial incidence, or the not infrequent history of dystocia, the collections of lymphocytes in the meninges and brain, the overgrowth of neuroglia or the vascular alterations within the lesion itself. In retrospect, it is somewhat amazing that these various facets of the problem could strike the individual investigators with such divergence. But it is not so surprising that some common cause was not suspected which would serve to unify so widely differing lesions on one etiological basis.

THE CONCEPT OF NEONATAL ANOXIA AS A CAUSE OF DEFORMING CEREBRAL LESIONS

The year following the appearance of the final folio of Cruveilhier's justly famous Atlas, an English surgeon named Little (1843)[18] reported a series of clinical observations on crippling deformities of the extremities in children and asserted that cerebral palsy was traceable in many instances to asphyxia at birth. Although these articles were reprinted in book form a decade later[19] and again as a separate report in 1861,[20] the seed he thus sowed fell on stony ground. Even a resowing of the idea by so illustrious a physician as Osler (1899)[27] did not come to harvest.

Instead, investigator-physicians became more and more impressed with the repeatedly told story of difficult delivery, and "birth injury" in its mechanical aspects came to be charged by one school with the responsibility for at least some of these lesions. This concept was brought into clear focus by the masterful studies of Schwartz (1924, 1927)[29, 30] who demonstrated what dystocia could do to the skull, the dura and the brain. Others have continued to point out this association, for example Norman (1944, 1947, 1949)[24, 25, 26] of England, and Benda (1945)[2] and Malamud (1950)[22] in this country. It remained to be shown that it was not the mechanical effects of dystocia that produced the residual lesions, but rather the respiratory failure consequent to increased intracranial pressure which, through resultant anoxemia, was actually responsible for these results (Courville and Marsh, 1944).[11]

A review of pertinent literature has brought to light much that supports this thesis. Grinker (1925)[15] suggested the similarity of the lesions in the demyelinizing diseases and disintegration of myelin after asphyxia from carbon monoxide poisoning. Others (Jedlowski, 1938;[17] Hurst, 1940;[16] Lumsden, 1950[21]) have seen resemblances between the central degenerations after cyanide poisoning and these same diseases. Some observers, noting the associated vascular changes in these conditions, attributed their genesis to some circulatory disturbance, and Morrison (1946)[23] concluded that the disturbance is caused by anoxemia.

If, indeed, unusual and divergent conditions such as Schilder's disease and status marmoratus can be explained on the basis of oxygen want, is it surprising that cerebral atrophy, both general and local, should result from this process? The experimental production of similar atrophic changes (Windle and Becker, 1942, 1943[33, 34]) by deprivation of oxygen to the fetal brain of animals on the one hand, and the observation of acquired lesions essentially identical to those of lobar atrophy of childhood (Friedman and Courville, 1941) on an ischemic basis (Spatz, 1926[31]), would seem to support this assumption.

If all this proves to be true, why is it that there has been so long a wait for an answer as to causes of these disorders, particularly since this group of lesions has been subject to the most critical inquiry? The difficulty has been, not that the various details of these diseases were not recognized; it lay in the fact that the various evil potencies of anoxemia for tissue damage were not understood. It did not occur to investigators that a key to the situation was at hand in the form of focal loss of nerve cells in the cerebral cortex (Herde), which is now recognized to be the characteristic effect of oxygen want,

whether generalized (anoxemia) or limited to the distribution of a given vessel (ischemia). It is also a fact that only recently has it come to be understood that the action of the cyanides in particular is dependent upon their interference with cellular oxygenation. Again, it was further not appreciated that the primary anoxemia sets up a chain reaction in the cerebral blood vessels, resulting in secondary vasomotor disturbances that accentuate, prolong and often localize the original effects of lack of oxygen. Only with this information at hand was it possible to explain certain delayed effects, such as demyelinization, which occurred long after the causative anoxic episode had taken place. Nor was it appreciated that even some tertiary effects (as for example, gliosis, status marmoratus, macrogyria) could occur as a consequence of destruction of inhibiting cells, tissues and structures. Once these truisms were grasped, it was but a step to apply them to the group of structural disorders whose genesis had hitherto been shrouded in mists of uncertainty.

ANOXEMIA AND OTHER CEREBRAL LESIONS

In view of experiences with the more profound degrees of anoxia after nitrous oxide anesthesia (Courville, 1936, 1938, 1939[5, 6, 7]), and with a full understanding of the vital necessity of intact cerebral circulation, the cortical and ganglionic alterations found after severe degrees of shock, prolonged cardiac standstill, and exsanguination are also properly understood as actual manifestations, albeit of different mechanisms, of anoxemia. And with a wider comprehension of the role of oxygen in the metabolism of nerve cells, the cellular and architectural changes consequent to hyperthermia (excessive demand for oxygen) and hypoglycemia (lack of glucose in the presence of abundant oxygen) are to be interpreted as disturbances in internal respiration, a form of anoxemia.

What other problems concerning brain disease does this information aid in solving? In the first place the mechanism of an entire group of lesions characterized by new formation of capillary blood vessels in the cerebral cortex becomes lucid. It is very likely that the focal red softenings in certain syphilitic disease (Huebner's syphilitic endarteritis), the circumscribed cortical scars in arteriosclerosis, the focal cortical lesions in rheumatic disease and pneumonia, and the cortical and ganglionic alterations in a whole bevy of poisonings with heavy metals, the alkaloids and hypnotic drugs, are to be accounted for by local circulatory changes leading to partial softening of the tissues. It is possible also that the secondary vascular lesions of the brain stem of alcoholic encephalitis belong in this same category. In gross vascular diseases it seems certain that local ischemias are responsible for these specific lesions. In the case of intoxications, it is suggested by histological findings that the noxious effects are felt by the endothelium of the blood vessels as well as by the nerve cells and that in event of occlusion of the capillaries incident to swelling of the endothelium, focal thrombosis or even hemorrhage and focal ischemia results, causing secondary softening which leads in turn to endothelial proliferation. These changes are also significant when they occur in the corpus striatum (as in barbiturate poisoning and lead poisoning) because of the known sensibility of this structure to oxygen want. The recent suggestion that Wilson's disease is a consequence of a disturbance of copper metabolism may account for both the attendant cortical and ganglionic lesions through some change in the blood vessels with secondary ischemia. It is, moreover, quitely likely that the alterations in the individual nerve cells in a number of exogenous intoxications (alcohol, barbiturates and narcotics as well as the cyanides) are actually the result of an interference with cellular oxidation (histiotoxic anoxia).

There are other clinical entities which possibly are owing to the effects of anoxia in one form or another. Some instances, at least, of mental deficiency (Berry, 1928[3]), idiopathic epilepsy (Nielsen, 1945; Courville and Nielsen, 1953[12]), certain of the psychoses (Batten and Courville, 1940[1]), some neuroses (Fletcher, 1945[14]), behavior disorders (Preston, 1945[28]), juvenile parkinsonism, and possibly some of the so-called abiotrophic and degenerative diseases of later life as well, may have their beginnings in long-forgotten paranatal anoxia. The reasons for these assumptions have been given elsewhere (Courville, 1950.[9]).

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Treatment of Intraoral Carcinoma

Combined Resection of the Jaw and Radical Dissection of the Neck

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• Intraoral carcinomas first occur as primary growths. From these sites they spread by the lymphatics to the regional nodes. In the past, treatment of these lesions has consisted of radiation therapy for the primary lesion, followed by radical neck dissection. The results of this treatment have not been satisfactory. On the other hand, for carcinoma elsewhere in the body the results of surgical extirpation of the primary lesion, of the intervening lymphatics and of the regional nodes at the same operation has given much better results.

In the past few years an attempt has been made to improve the results of treatment of intraoral carcinoma by removal in continuity of the primary lesion, intervening lymphatics and regional nodes. The improvement in anesthesiology, electrolytes and fluid balance, blood replacement, and the development of the antibiotics, in conjunction with the realization that the cosmetic deformity is not as great as might be expected, has led to this development. In those centers where it has been possible to apply this principle of treatment to intraoral carcinoma the results have been very encouraging.

ANY RATIONAL TREATMENT of intraoral carcinoma must be based on a sound understanding of the natural history of the disease. At their inception, all such lesions are microscopic in size. They are confined to the area of the first appearance and remain there an indeterminate time, finally metastasizing. This spread takes place at different stages of growth depending on the type and grade of tumor. The path of spread of a primary intraoral lesion beyond the site of origin takes place with such a regularity of pattern, in almost all cases, that it is predictable within a narrow range of error. From a lesion located definitely to one side of the midline, as most are, extension is almost always to the cervical lymph nodes on the same side. Very rarely, metastasis to the opposite side occurs.

Once present in the nodes, the carcinoma will be confined there for a variable period, again depending upon its rate of growth. If untreated, or inadequately treated, the disease will finally spread beyond the limits of the cervical lymphatic system and kill the patient. Obviously, with a means of therapy that would eradicate the primary lesion, the regional lymph nodes, and the intervening lymphatic channels at the same time, before the disease became inoperable locally, more patients with intraoral carcinoma could be successfully treated. Indeed, that is a fundamental principle of surgical treatment of cancer.

In postmortem examination of patients who died of intraoral carcinoma, it was observed that the disease in at least 80 per cent of cases remained confined to the limits of the head and neck.[1, 10] Death in those cases was caused by inanition, hemorrhage, respiratory distress, or infection. In only a very small minority of cases was spread of the disease to distant areas noted at autopsy—a stirring challenge to physicians treating intraoral carcinoma.

With that principle followed in abdominal perineal resection for cancer involving the intestinal wall, various investigators have reported five-year "cure" rates of 65 per cent,[3] 43 per cent[4] and 90 per cent[6] in cases in which there was spread beyond the serosa but no palpable lymph nodes. The "cure" rates in cases in which there was lymph node involvement were 20 per cent, 23 per cent and 37 per cent, respectively. The five-year survival rate after the standardized radical mastectomy (based on the same principle) when performed in cases where no regional nodes were palpable was 81 per cent,[6] compared with 59.3 per cent in cases in which the lymph nodes were involved. As to results of treatment of cancer of the bucca, gingiva, tongue and floor of the mouth, the five-year "cure" rate has been variously reported as from zero to 20 per cent in cases in which adjacent nodes were palpable and from 28 to 50 per cent when there was no clinical evidence of extension to the nodes.[7, 8, 11]

Since intraoral cancer certainly is no less accessible than cancer of the breast or of the lower gastrointestinal tract, question arises as to the inferior results of treatment. It has been promulgated, by oncologists, that the greatest part of the answer can be found in the method of treatment that has been

used for intraoral cancer: In almost all cases, radiation to control the primary lesion, then, four to eight weeks later, radical dissection of the neck on the side of the lesion, in some cases because metastases were present and in others as a "prophylactic measure." Thus, the previously mentioned basic principle of surgical treatment of cancer has been violated.

The lymphatic channels between the primary site and adjacent nodes cannot be ignored. Channels from the tongue, the floor of the mouth, the alveolar ridge, and the buccal mucosa pass into the periosteum of the mandible and some of them enter the bone, and tumor cells that remain within them can progress to any of those sites.

In an attempt to solve these problems of intraoral carcinoma, combined jaw resection and neck dissection in continuity has been increasingly performed in the last five or six years. The en-bloc removal of the primary intraoral lesion, the intervening lymphatic channels and the regional nodes was known many years ago. But the mortality rate incident to the operation was high and, what with the rapid advances that were made in roentgenologic technique, radiation became the treatment of choice. Now, however, increased knowledge of fluid and electrolyte balance, blood replacement and the use of antibiotics has made possible the performance of so radical an operation with very low mortality.

The technique of the procedure for removal of a primary lesion, the regional nodes and the intervening lymphatic channels has become rather well standardized, and description of it in great detail may be found in any of several papers.[2, 12] For a carcinoma of the tongue, half the tongue and the floor of the mouth on the involved side, as well as the mandible and all lymphatic and node bearing tissue on that side of the neck, must be removed. For a clean dissection this will include all tissue removed in a standard radical neck dissection as outlined by Martin.[9]

The procedure is not so deforming as might be thought. There is some flattening of the face on the side operated upon, but if the remaining mandible is immobilized in the proper plane of occlusion for six to eight weeks, until scar contracture has occurred, it will be maintained in a relatively normal position and not pulled grotesquely to one side. Ability to open and close the jaw and to masticate acceptably can be expected.

The worth of any procedure in the treatment of carcinoma is measured by the results. Reports by surgeons who have done the operation on many patients indicated that five-year "cure" can be expected in 40 to 60 per cent of cases.[9, 12] These reports are the more remarkable in that they are based on the results obtained in quite advanced cases. As would be expected, combined jaw resection and neck dissection was first applied only when there appeared to be nothing to lose. In light of the results in such cases, indications for use of the operation in more favorable circumstances are constantly being extended. Some physicians feel that the problem of intraoral carcinoma should be approached with the same attitude as is carcinoma of the breast. In dealing with mammary cancer, surgeons do not hesitate to remove the primary lesion, the intervening lymphatic channels and the regional nodes with sacrifice of all associated tissue, even in cases in which there is no clinical indication of involvement of the nodes.

At present the philosophy of combined jaw resection and neck dissection and the indications for the operation are in a state of development and flux. Physicians most familiar with the problems of dealing with the condition are rather generally agreed that the procedure should be applied if there is enlargement of the nodes in the neck. The final status and application of this procedure will have to be developed in centers where there are many cases and enough data for statistical analysis can be collected in a relatively short time.

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Diagnosis and Treatment of Gouty Arthritis

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• The characteristic phenomena of acute gouty arthritis are acute arthritis in a middle-aged male, associated with serum uric acid above 6 mg. per 100 cc. and a satisfactory response to colchicine. Roentgenographically observable changes do not occur early.

In recent years uric acid metabolism has been studied by means of isotope techniques utilizing labeled substances. Uric acid is excreted in relatively constant amounts by humans and is little affected by variations in dietary intake, except for purine or nucleic acid substances. Persons with gout have a greater total amount of uric acid and a lower turnover than normal persons.

In the treatment of acute attacks of gout colchicine is still the most practical single drug, even though its pharmacologic action remains unknown.

Benemid (probenecid) is a powerful uricosuric agent of low toxicity which has been subjected to extensive clinical trial for three years. It causes inhibition of the resorption of urate from the glomerular filtrate; the site of action is believed to be the tubular cells. The author's usual dose is 2 gm. a day. This has caused a lowering of the uric acid in the serum and an increase in the urinary output.

AN ADEQUATE UNDERSTANDING of the approach to the diagnosis of a clinical entity and an effective regimen of therapy should be based upon accepted concepts of normal and abnormal function. Diseases that are identified as metabolic disturbances serve as good examples. Although gout is not the example par excellence, a clinical discussion of this dyscrasia may be developed from accepted physiological and biochemical phenomena.

The clinical finding of acute arthritis associated with the cardinal signs of inflammation in a male should suggest gout as one possibility. If it is present the amount of uric acid in the serum will be above 6 mg. per 100 cc., and if a "full course" of colchicine is administered, the acute articular symptoms should subside. These items—a characteristic clinical picture, an elevation of serum urate and a satisfactory response to colchicine—constitute the triad of acute gouty arthritis. Elaboration and extension of these phenomena will constitute the basis of this discussion.

The initial attack of acute gouty arthritis usually appears in the middle decades of life but it may appear as early as the first decade or as late as the eighth. The disease affects males predominantly; fewer than five per cent of patients are females. So infrequently does the disease occur in females that a clinician must exercise unusual acumen in making a diagnosis of gout in a female if subcutaneous tophi have not developed. About two-thirds of a series of patients observed by the author had a family history positive for gout. This datum frequently is helpful in diagnosis during the earlier years of the disease if stigmata of the well-developed case of gout are lacking. Acute attacks are likely to affect the metatarsal-phalangeal joint of the great toe, but they may involve any joint or joints in the upper or lower extremities. If the central joints of the body are afflicted, tophaceous deposits usually have developed and the diagnosis is not in doubt.

Acute gouty arthritis may appear following the impact of one of several precipitating agents or it may appear spontaneously. An acute infection, a surgical operation, meteorologic changes, emotional turmoil, one of several drugs which include a mercurial diuretic and antibiotics, particularly penicillin and the vitamin B preparations administered parenterally, have been so implicated. The suddenness in onset and the severity of pain in a previously asymptomatic male are typical. Complete restoration of function may be expected if chronic deforming articular changes are absent.

Observation of a concentration of uric acid in the serum is of considerable help in diagnosis if properly determined, but may be misleading in selected instances. The determination in the routine biochemical laboratory is more difficult than several of other routine procedures. Uricosuric agents such as sodium salicylate, cinchophen, corticotropin (ACTH) and Butazolidin® are anti-arthritic agents that may depress an elevated urate concentration and cause

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confusion. Known uricosuric agents should be omitted for at least 48 hours if diagnostic information is sought regarding the concentration of uric acid in the serum.

The response to a "full course" of colchicine is highly specific. No other disease of the joints responds so well to this drug. The other anti-arthritic drugs which include sodium salicylate, corticotropin and Butazolidin are endowed with limited diagnostic capacity. A "full course" of colchicine will be described later.

Conditions other than gout which may be associated with increased concentration of serum urate include acute febrile illness, renal insufficiency, leukemia and selected other blood dyscrasis. It is noteworthy that increased concentration of uric acid in the serum occurs relatively often in non-arthritic relatives of gouty patients. Furthermore, in a series of "normal" persons a small proportion may show an increased concentration of serum urate that is not explained satisfactorily. The determination of serum urate in a multiphasic screening project as a public health effort is to be encouraged.

Roentgenographic evidence of articular disease is not an early finding in patients with gout. A decade or more may elapse following the initial attack of acute gouty arthritis before the characteristic roentgenographic changes are present. Not infrequently in a mild case of gout no changes will be noted in unmagnified images throughout the natural life of the patient. With the development of a satisfactory technique for magnified roentgenography, characteristic changes may be detected in some patients at an earlier stage of the disease.

Circumstantial evidence suggestive of gout includes low grade albuminuria, hypertension, large vessel sclerosis and urate calculi. It is not believed that coronary sclerosis in the absence of articular gout is intimately related to the metabolic dyscrasia.

The increased concentration of uric acid in the serum reflects a similar concentration in the synovial fluid and probably other interstitial fluids except those associated with the central nervous system. The mechanism by which increased concentration of uric acid in body fluids is brought about is not known but certain presumptions have been advanced. There are at least three reasonable possibilities to account for the increased concentration: Decreased destruction, impaired excretion or increased formation.

There is meager evidence only that gouty patients are deficient in uricolytic enzymes. The only experimental data in this regard indicate that there is no difference between a gouty and a non-gouty subject with regard to destruction of preformed uric acid. Impairment of excretion of uric acid to the kidney received considerable attention before the modern concept of renal function was widely accepted. At the moment it is believed that uric acid appears in glomerular filtrate in essentially the same concentration as it exists in a protein-free filtrate of plasma. The glomerular filtrate is acted upon by the tubular cells and approximately 90 per cent of the urate is resorbed and only 10 per cent is excreted in bladder urine.

If expressed in functional terms, the urate clearance is approximately 10 cc. per minute. This implies that the quantity of uric acid contained in 10 cc. of plasma is excreted from the body in this unit of time. This may be compared in a controlled experiment with the clearance of water of 2 cc. per minute and the clearance of urea of 65 cc. per minute. If 10 per cent of uric acid that appears in glomerular filtrate is excreted and 90 per cent is resorbed, it might be in the realm of possibility to alter this proportion by interfering with tubular resorption. The uricosuric agents noted above are believed to act in this manner. Furthermore, it has been demonstrated that when the sugar content of the blood is high—400 mg. per 100 cc. or greater—the tubules are saturated and working maximally in resorbing glucose from glomerular filtrate and the excretion of urate is enhanced. It has been postulated that in such circumstances the resorption of glucose takes precedence over resorption of urate and for a time the tubules do not extract the usual amount of uric acid.

In recent years another phase of uric acid metabolism has been approached through the use of isotopes, radioactive and heavy isotopes alike. Selected studies in humans and in animals utilizing labeled substances have shed considerable light upon the precursors of uric acid. It has been known for some time that uric acid is the end-product of nitrogenous substances of amino acid and pyrimidin origin. Most other mammals convert uric acid to allantoin and excrete only small amounts of uric acid. Birds and reptiles excrete uric acid as the end-product of nitrogenous substances whether of purine or amino acid origin.

Uric acid is excreted in relatively constant amounts by humans and is little affected by variations in dietary intake except for purine or nucleic acid substances. At least 300 mg. of nitrogenous urate is excreted daily on a purine-free diet with an adequate caloric intake.[11] It is generally accepted that mammals are capable of synthesizing purines as well as of converting purines to uric acid. It has been shown only recently, however, that some of the simpler biological substances such as carbon dioxide, formic acid, lactate, acetate, glycine and serine contribute a nitrogen or a carbon atom to the uric acid molecule in the intermediary metabolism of the substance. The observation that some of these sim-

pler biological substances may stem from carbohydrates or fats as well as proteins and purines should affect the thinking regarding the dietary regimen for patients with gout.

Another isotope technique that has been used by a few laboratories in recent years for the study of uric acid metabolism and the gouty dyscrasia is the uric acid molecule tagged with heavy nitrogen (N^{15}). The uric acid molecule with two isotopic nitrogens may be synthesized in the laboratory and injected intravenously into experimental subjects. From 25 to 100 mg. of the purified labeled uric acid may be injected as a neutral solution without untoward effects. Complete urine samples are then collected for a period of approximately one week. The uric acid is isolated, broken down and the determination of the ratio of N^{15} (heavy nitrogen) to N_{14} (naturally occurring nitrogen) is made in a mass spectrometer. The information gained permits calculation of the total amount of uric acid that is freely diffusible within the body at the time of the injection. Obviously certain assumptions are necessary but the results are quantitative and have been confirmed in several laboratories.[2] The metabolic pool or miscible pool of uric acid for a normal person ranges from 900 to 1,300 mg. and the turnover rate of pools ranges from 0.6 to 0.9 times per day. Patients with gout, on the other hand, have a metabolic pool that is two or more times greater than the normal and a turnover rate that is appreciably less.

The significance of the mathematical calculations derived from these isotope experiments is not defined clearly. The rapidity with which uric acid enters and leaves the miscible pool as measured by the turnover rate, however, is in keeping with the metabolic exchange of other biological substances as measured by isotope techniques. The metabolic pool probably does not take into consideration deposits of uric acid in soft tissue and bone. The technique is an expensive and a laborious one for each experiment and does not lend itself to a large number of experimental subjects or a large number of therapeutic agents. Undoubtedly the determination of the miscible pool and turnover rate would be a good diagnostic tool if it could be applied widely. It probably is the most reliable diagnostic laboratory procedure in the pretophaceous stage of the malady. Fortunately it is not necessary to resort to this procedure in order to reach a presumptive diagnosis.

The action of drugs on the miscible pool and on the turnover rate has been studied in a few instances as noted below but other antirheumatic preparations might be investigated with this technique. What action precipitating agents may have upon the metabolic pool has not been investigated nor has a series of non-affected relatives of gouty patients been so investigated.

Adequate treatment of acute attacks of gout is not understood as generally as deserved. Even physicians who have the disease show less than maximal appreciation of the proper therapeutic regimen. Colchicine or a preparation containing colchicum has been recommended for almost six centuries for the treatment of the acute stage. Colchicine remains the single most practical drug, in the author's opinion.[3] In the introduction of this discussion the hope was expressed that diagnosis and therapy would be based upon physiological and biochemical principles. Colchicine is an exception to this hope. The pharmacologic action of colchicine is not known. The use of colchicine is purely empirical. No consistent effect upon the concentration of uric acid in the serum or the excretion of uric acid in the urine following the administration of colchicine has been demonstrated. Nor does colchicine alter appreciably the miscible pool of uric acid or the turnover rate. It is nevertheless a powerful and valuable drug in the treatment of gout. Colchicine is available in 0.5 mg. tablets and need not be administered with a complementary drug such as salicylate. The ingestion of one tablet (0.5 mg.) every hour or two tablets every two hours should begin at the earliest sign of acute articular distress. If the attack proves to be mild, then not more than four or six tablets need be taken. If the attack is severe or even moderate, ingestion should continue until a "full course" has been taken. This varies between 8 and 14 tablets.

The measuring stick for an adequate number of tablets is the onset of gastrointestinal distress—nausea, vomiting or diarrhea. When that occurs, colchicine is to be stopped and a gastric sedative taken. Tincture of camphorated opium, 5 cc., constitutes the second phase of the "full course" and doses of that amount should be taken every two hours until the untoward symptoms subside. Response to a "full course" of colchicine is adequate in most instances if begun early. In an inadequately treated acute attack or an acute attack that has not responded maximally, a second course may be necessary after a lapse of 48 hours. It is unwise to begin a subsequent course sooner because of intolerance of the gastrointestinal tract.

Colchicine is a safe preparation to use and the incidence of serious toxic effects is lower than that with other anti-gout remedies such as cinchophen, corticotropin and Butazolidin. The carcinogenic action of colchicine which has been demonstrated in plants bears no clinical significance to the use of colchicine in humans. In order to demonstrate a carcinogenic action in plants, the amount of colchicine that must be applied is, relatively, as much as one hundred times the therapeutic dose for gouty patients. Over a period of almost two decades the incidence of cancer in patients observed by the author appeared to

be no greater in those who took colchicine at frequent or infrequent intervals than in a similar number of normal or non-gouty persons. There is no objection to giving codeine or other analgesics during the first few hours after the institution of the colchicine regimen. Also a drug to induce sleep may be given at bedtime. Frequently this enables the patient to return to sleep after each dose of colchicine if the course is continued during the night.

There are indications for the intravenous use of colchicine in selected instances. The author uses it thus to complement or to supplement partially the oral route but not to replace it. It is believed that patients should not be dependent upon an intravenous medication at frequent intervals if the oral route will suffice. A few patients with advanced chronic gouty arthritis who have frequent attacks of acute gout may rely upon the intravenous route because of the apprehension of possible gastrointestinal distress. Intravenous injection is also helpful in treatment of gout in a patient with a peptic ulcer or a chronic disturbance of the colon such as colitis or diverticulitis, for such a person may become intolerant prematurely to a "full course" of colchicine by mouth. In either instance, approximately half of the "full course" is given by the oral route and the remainder intravenously. Sufficient intravenous colchicine (1.0-2.0 mg.) may be given at a single injection to complete a "full course" without causing the gastrointestinal distress that might result from ingestion of a similar quantity near the end of the course.

Butazolidin is believed to be a drug of second choice for the treatment of an acute attack, although several rheumatologists prefer it.[7] In some instances a more rapid response has been reported than that which follows a course of colchicine if Butazolidin (200 mg.) is administered every three or four hours for several doses. In the author's experience, adequate recovery is no more rapid following Butazolidin than following an adequate quantity of colchicine. The one advantage of Butazolidin is that, with it, gastrointestinal irritation is minimal or absent. On the other hand, when Butazolidin is administered daily for a period of days, it may cause serious side effects, particularly upon hematopoiesis. It is believed that further experience will be necessary before the proper place of Butazolidin in the treatment of acute gout can be determined.

Only a short time ago corticotropin was believed to be the drug that might replace colchicine for treatment of an acute attack. Surely dramatic results followed in some patients the intramuscular administration of from 60 to 120 mg. of corticotropin in one or more doses. Other patients showed little or no response to this preparation. In addition to the disadvantages of any preparation that must be administered by the parenteral route, frequently there is recrudescence of articular symptoms two or three days after the last dose of corticotropin.[9] If colchicine is ingested at the same time that corticotropin is administered and continued for two or three days, the return of acute arthritis may be prevented. Thus if corticotropin is administered, probably the best plan is to give submaximal doses of colchicine (1.0 to 2.0 mg. daily) during and after hormonal therapy. It is the author's practice to reserve corticotropin for exceptional instances in which patients are intolerant of colchicine and are in urgent need of treatment for acute symptoms. Cortisone has proved disappointing in the routine handling of patients with acute gouty arthritis and need not be discussed.

Salicylates and cinchophen have been widely used as anti-gout agents but neither is specific nor is either as effective as colchicine in the treatment of acute attacks. The analgesic effect together with the uricosuric action is evidence of some merit. Cinchophen should not be confused with colchicine although pronunciation and spelling are similar. Cinchophen is not recommended, for there are other preparations that are believed to be superior and less toxic. Nor are salicylates used routinely by the author. If they are considered desirable 1 gm. of sodium salicylate may be ingested two or three times a day.

General measures for the treatment of acute gout should be based upon recognized principles of counteracting local and systemic effects of acute arthritis as well as of acute inflammation. A light diet and an abundant intake of fluids together with rest of the affected joints seem obvious. No useful purpose is served if severely affected joints are kept active or subject to weight bearing. If not more than one or two joints of the upper extremities are involved, the application of an arm sling may permit continued ambulation. Restriction to a chair or bed is desirable if one or more joints of the lower extremities are severely afflicted. Tight shoes should be avoided during the day and a cradle for the bed covers used at night if the feet are involved in acute arthritis. Local application of moist dressings, dry heat or cold compresses may have limited value.

Gout between acute attacks is as susceptible to therapeutic agents as it is in the acute state. Although no effect upon uric acid metabolism may be attributed to colchicine, the periodic use of this preparation in the intercritical period has been found to be extremely useful.[10] The author recommends some colchicine in the intercritical period. If the patient has less than one acute attack a year, one colchicine tablet (0.5 mg.) two or three times each week is prescribed. The indirect benefits may be more important than any direct benefit. A patient in whom gout is suspected, on the basis of at least one attack of acute arthritis, is a potential candidate for subse-

quent attacks. If colchicine tablets are taken from time to time, a supply is readily available when articular symptoms return. It is also believed by the author, without the support of statistical evidence, that some local benefit accrues from periodic ingestion of colchicine.

A patient who has more than one acute attack of gouty arthritis a year is considered to be moderately or severely afflicted, the degree depending upon the amount of chronic irreparable damage to the joints and the stage of the natural course of the disease as well as incidence of acute symptoms. The ingestion of at least one tablet a day (0.5 mg.) is recommended for moderately afflicted patients and a slightly higher dose for those in whom the disease is more severe. Tolerance of the gastrointestinal tract usually is the determining factor in establishing the dosage to be given for maintenance of severely afflicted patients —as more than 15 per cent of patients with gout are. A few patients may tolerate and benefit from as many as four colchicine tablets each day of the year. Others may alternate between two and three and four tablets daily. Moderately and severely afflicted persons who follow such a regimen have fewer acute attacks and a sense of well-being. The effect of the drug does not diminish through continuous use; if an acute attack develops, a "full course" of colchicine is maximally effective, irrespective of previous ingestion. Exception must be made in the case of a patient who is on the borderline of gastrointestinal irritability from the daily ingestion of maintenance dosage; in that situation, vomiting or diarrhea may occur before a "full course" for an acute attack can be completed. Hence it is important that the quantity of colchicine ingested daily be not more than the intestinal tract will tolerate. Another obvious gain from the ingestion of colchicine daily is the advantage of having started a "full course" at the earliest possible moment should acute symptoms appear. The number of patients with gout who have taken colchicine daily for a decade or more is sufficiently large that it can be stated with assurance that such a regimen is beneficial and is not associated with undesirable features. Until such time as more effective drugs are discovered or effective means of correcting the disturbance of uric acid metabolism are devised, it is believed that colchicine should be an integral aspect of the treatment during the intercritical period.

A powerful and a non-toxic uricosuric agent to complement the use of colchicine during the intercritical period has been one of the aims of investigators of the metabolic dyscrasia for a long time. Until recently cinchophen and salicylates were the only uricosuric agents available. The disadvantages of these preparations have been mentioned. During the past three years a new preparation, Benemid® (probenecid), has been subjected to extensive clinical trial. Benemid is a powerful uricosuric agent which exerts its action soon after ingestion.[3] It is a substance of low toxicity when administered daily in therapeutic amounts. The site of the uricosuric action is believed to be the tubular cells and the resorption of urate from glomerular filtrate is inhibited. The urate clearance as measured by 24-hour urine specimens may be increased to 15 cc. or higher. The increase in the amount of uric acid excreted each day may be from 30 to 50 per cent in patients who are ingesting 2.0 gm. of Benemid daily. Although the maximum action of Benemid upon the concentration of uric acid in the serum may be apparent during the first few days after the beginning of ingestion, a pharmacologic action is never abated and in most patients the action may be demonstrated so long as the drug is administered daily. The author gives 2.0 gm. of Benemid daily; other investigators prefer a slightly smaller dose.[4, 8] Most patients tolerate the larger dose without gastrointestinal distress. The author has proceeded on the assumption that the larger the quantity of Benemid ingested, without causing gastrointestinal distress, the greater the uricosuric action and the greater the inhibition of the tendency for precipitation of urate in bony and soft tissues. Several patients observed by the author have been taking Benemid for three years. One of them was studied for a three-year period before Benemid therapy was begun. During the control period the concentration of uric acid ranged between 7.5 and 10.5 mg. per 100 cc. of serum. Soon after the ingestion of Benemid was started the concentration decreased to less than 4 mg. per 100 cc. and thereafter varied between 4 and 4.5 mg. In each instance when the concentration was determined, it was below the lower range for gouty patients. Increased excretion of uric acid in the urine, which occurred concomitantly, was probably the cause of the decrease in the amount in the serum. When determined from time to time in the period before Benemid was given the daily excretion of uric acid was approximately 650 mg. A maximum of 1,700 mg. was excreted on the first day of Benemid therapy. After the first week of ingestion of Benemid, the daily amount fluctuated between 900 and 1,500 mg. When last determined, approximately two years after the beginning of treatment with Benemid, it was 1,050 mg.

The third metabolic function influenced by Benemid—this determined in only a few patients—is the metabolic pool of uric acid. When Benemid was given, a significant decrease of the metabolic pool occurred, similar to the decrease observed by Benedict and Forsham[1] following salicylate therapy. However, when administration of Benemid was discontinued, restoration to the normal range was not

observed. On the other hand, an increase to the normal range in the turnover rate did occur, which suggests that Benemid may have some effect upon the intermediary metabolism of uric acid. However, the general consensus is that the only effect is upon the transport of uric acid through the tubular cells.

The clinical benefits associated with administration of Benemid, although it takes some time for them to develop, are encouraging. At first, acute attacks of gouty arthritis occur during Benemid therapy just as they had occurred before administration of the drug was started. In some patients there may be a slightly greater incidence of attacks during the first few months of treatment with Benemid. Subsequent experience may invalidate this impression. It is a clinical observation, however, that acute attacks of gouty arthritis of the same severity appear immediately after the beginning of treatment with this new drug. Meanwhile, the concentration of uric acid in the serum may be within the normal range. This confirms the impression stated some years ago that the absolute level of uric acid in the serum is not the determining factor in the pathogenesis of acute attacks of gouty arthritis. From four to six months after Benemid therapy is started, there appears to be a lessening in frequency of acute attacks. Thereafter the diminution in severity and frequency is reassuring. In addition, the majority of patients have an improved feeling of well-being not noted while colchicine was the only drug administered regularly.

The toxicity of Benemid was not a significant clinical problem in the series of patients observed by the author. A few patients reported minimal gastrointestinal distress when tablets were taken at frequent intervals with the stomach empty. On the other hand, if the single doses were spaced at longer intervals throughout the waking hours, symptoms of this side action usually were not observed. The tablets should be taken with food and not on an empty stomach. Two patients noted a skin rash. In four instances urate stones were passed by patients who were taking Benemid, but the incidence of this phenomenon (15 per cent) was no greater than it is in all gouty patients.[6] Undoubtedly the increased excretion of uric acid in the urine augments the tendency, but to date it has not been a serious clinical problem and in no instance was Benemid discontinued permanently because of the passage of a urate stone. One patient that was observed in a neighboring clinic had a severe anaphylactic reaction when given a very small amount of Benemid. The observation has been confirmed and the validity must be accepted. An abundant fluid intake is desirable for most patients with gout, and continued vigilance in this regard should be stressed if Benemid is taken.

The ultimate benefit from the uricosuric action of Benemid remains to be determined. It is believed that a period of several years must elapse before the advantages as well as the disadvantages will be defined. The longer Benemid is used, the less the apprehension regarding the development of untoward symptoms and the greater the hope of persistent good. Since Benemid stores the concentration of uric acid to the normal range or returns it toward the normal range, decreases the metabolic pool and increases the turnover rate, it is probable that a reverse migration of urates from articular deposits to the miscible pool occurs and that subsequently the urates are discharged from the body by way of the kidneys. Furthermore, since it probably takes years for urates to be deposited in gross amounts in and about joints, undoubtedly a reversal of this abnormality takes a long time also. In the patients observed by the author, no changes were noted roentgenographically until after at least 18 months of Benemid therapy. Other observers have reported regression of subcutaneous or osseous tophi in shorter periods.[5] Until such time as conclusive observations are made in support of regression of the metabolic dyscrasia, colchicine in addition to Benemid should be prescribed routinely during the intercritical period.

There are few clinical data in support of the contention that cortisone, corticotropin or Butazolidin are desirable agents for use daily or at regular intervals in the intercritical period of chronic gouty arthritis. The analgesic action of either of these preparations for low grade symptoms can probably be achieved with other therapeutic agents if it is so indicated. A uricosuric action can be accomplished more effectively by Benemid. Thus it is believed that no one of these preparations is indicated for periodic use in the intercritical period.

Another measure in the treatment of patients with gout is dietary control. An abundant intake of water is highly desirable. Since the concentration of uric acid in body fluid and glomerular filtrate is near the saturation level, the tendency for urates to precipitate in bone and soft tissue as well as in the tubules during the resorption of fluid from glomerular filtrate, which is out of proportion to resorption of urate, poses a threat. Any measure which minimizes this tendency is desirable. Tap water should suffice in most instances. Fluids with caloric supplements may be contraindicated since gouty patients have a tendency to gain weight. A patient with gout should develop the habit of drinking liberal quantities of tap water or alkaline water at meal time as well as between meals. The quantity consumed in the evening should be regulated lest nocturia become a problem. There is only meager evidence that alcoholic beverages, consumed in moderation, aggravate the meta-

bolic disturbance. In an occasional case there may be evidence strong enough to indict a particular alcoholic beverage as an inciting agent for acute gouty arthritis, and in that event it, in particular, should be avoided. On the other hand, most patients with gout can ingest alcohol temperately yet remain free of symptoms provided they do not neglect prescribed anti-gout measures. It is believed that in general any harm done by alcoholic beverages is owing to the amount rather than to the kind ingested.

The undesirable effects of purine foodstuffs have been noted on theoretical grounds for many years. The clinical literature on gout abounds in references to the subject. It is fortunate that several of the foodstuffs particularly high in purine content may be avoided without making a dietary invalid of a gouty patient. Although not reported to be as harmful as purines for patients with gout, proteins, particularly red meat, have been subjected to scrutiny. Many diets for patients with gout permit little or no red meat because of the possible exogenous and endogenous sources of uric acid. Studies by means of isotope techniques during the past few years have identified some of the precursors of uric acid, as was noted earlier in this discussion, and have removed some of the stigma from proteins. Recent observations in laboratories suggest that carbohydrates and fats, as well as proteins and purines, may be precursors of uric acid. The therapeutic implications regarding dietary restrictions for gouty patients are affected by these experimental data. Since carbon dioxide, formic acid and acetate contribute to the uric acid molecule, it is apparent that carbohydrates as well as proteins and fats in the diet are potential precursors. It is reasonable to assume, however, that some amino acids may contribute to the uric acid molecule to a greater extent than others. Laboratory evidence on this point is desirable.

The potential harm from a liberal intake of protein is believed to have been emphasized unduly. It is not generally appreciated, however, that proteins and certain nucleoproteins that yield pyrimidin base form urea, not uric acid, as the nitrogenous end-product. It is believed that a moderate intake of protein is permissible for patients with gout except in the presence of gross renal insufficiency. Restriction of proteins for such patients spares the kidneys the burden of excreting nitrogenous products generally. Such restriction does not necessarily imply that protein foods have a detrimental influence *per se*. Foods high in purine substances should be avoided at all times. These include meat extract, calf brain, anchovies, herring, spleen, liver, kidney and tongue. A high fat diet should be avoided for two reasons. It may precipitate an acute attack of gout as well as contribute to obesity. A patient with gouty arthritis who is overweight is putting a greater strain than is necessary upon weight-bearing joints. An obese gouty patient should avoid a high carbohydrate diet although there is little evidence except as noted above that carbohydrates are primary offenders.

In conclusion it may be stated that the proper use of a few selected anti-gout drugs will accomplish much in the control of the metabolic disturbance as well as the articular distress while temperate rules of eating and living should contribute generally as well as specifically.

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The Sublingual Administration of Curare

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• A new method of administering d-tubocurarine transmucosally by sublingual pellets (and also by rectal suppository) was used in 100 patients. In therapeutic dosage of 6 to 12 mg., it was found to be non-toxic and very effective in relieving pain due to acute and chronic muscle spasm. The relief was often of long duration or permanent and no unpleasant side effects were noted in any case. The drug was found to be more prompt and more effective in its action than mephenesin.

In addition to relief of pain, it was found to be useful in distinguishing between kinds of pain and hence in differential diagnosis.

CURARE, administered by injection, is now a well established drug in modern medicine. Clinical experience has confirmed experimental evidence that its toxicity is low in an effective dose range when adequate ventilation is maintained. Its first modern clinical use in neuropsychiatry to mitigate the convulsions incident to shock therapy was soon overshadowed by its employment in anesthesiology to enhance the relaxation of the skeletal musculature during anesthesia.

The first clinically adequate curare introduced by Gill, prepared by Squibb, and used by Bennett, was a solution of the whole drug known as Intocostrin.® The active principle of curare is d-tubocurarine and most present day preparations contain only this alkaloid.

Relatively short duration of drug action is desirable where curare is indicated in anesthesia and neuropsychiatry. For this purpose, the intravenous method of administration is ideal. Quite another circumstance prevails when curare is used in the treatment of acute or chronic diseases in which spasm of the voluntary muscles is a feature. Here a long continued but predictably lower level of curarization is desirable.

Fuller[4, 5] reported on the clinical use of a slow-release preparation of curare whose safety in animals had been established by Neff. This preparation contains 25 milligrams of d-tubocurarine per cubic centimeter and is given intramuscularly in doses of from 1 cc. to 1.2 cc. daily. A nurse once gave one ampule instead of 1 cc. to a none-too-robust patient. This was 125 mg. or five times the therapeutic dose. The patient was well relaxed, but had no ill effects and at no time was artificial respiration necessary. This affords an example of the relative safety of the slow-release preparation. Fifteen milligrams of an aqueous preparation of d-tubocurarine given intravenously to that patient probably would have resulted in respiratory arrest. The safety of the slow-release preparation of d-tubocurarine has been established insofar as danger to life from over-curarization is concerned.*

Clinicians have complained that some patients show evidence of a more rapid release of d-tubocurarine during muscular exercise, such as walking. It would seem that with the increase in circulation incident to walking, more d-tubocurarine is released from its intramuscular depot. Patients so affected would complain of great muscular weakness, diplopia, or both.

There are certain other shortcomings that are inherent in the injection of any drug in a repository medium. These include the necessity for the patient to present himself at the physician's office for the injection, and the possibility of an allergic reaction from the components of the menstruum.

The idea of sublingual administration of curare originated with Erdei of Toronto[1] who suggested it to Ferguson,[3] professor of pharmacology at University of Toronto. Ferguson held out little hope that the sublingual administration would be effective, since Walton's[9, 10] work had demonstrated that substances with low lipoid solubility are poorly absorbed sublingually. Ferguson said he still considered it likely that the effects produced by sublingual administration may be due to absorption lower down in the gastrointestinal tract, although he concluded that "such thoughts are not of great practical importance, because the sublingual method of administration seems to work remarkably well."

The first preparation used by the authors was in the form of sublingual pellets† formulated to contain 2 mg. of Gill's d-tubocurarine[4, 5] per pellet. The pellets now being used represent an advanced and different formulation by Gill. They contain 3 mg. of

*Since this time another almost identical accident occurred with the same outcome.

†NOTE: The pellets, suppositories, and chemically pure d-tubocurarine used in this study were made available by Richard C. Gill, Cugil Laboratories, Inc., P. O. Box 281, Palo Alto. These pellets and suppositories are now known as Tubalex.

TABLE 1.—*Transmucosal curarization. Biological establishment of safety indices for d-tubocurarine sublingual pellets (3 mg. each) and rectal suppositories (3 or 5 mg. each) by aberrant administration routes.*

Dosage Form of Tubalex	Animal*	Route of Administration**	Maximum Actual Dose Administered: mg./kg.†	Maximum Theoretical Dose: Mg./70 kg. Human‡	Observed Response
Pellets	Dog	Ingestion	22.5	1,575.0	0
Pellets	Rabbit	Ingestion	19.8	1,386.0	0
Pellets	Guinea pig	Ingestion	27.9	1,953.0	0
Pellets	Rabbit	Rectal, by "overloading"	2.05	143.2	0
Pellets	Guinea pig	Rectal, by "overloading"	12.5	875.0	0
Suppositories	Rabbit	Rectal, by "overloading"	5.08	355.6	0
Suppositories	Guinea pig	Rectal, by "overloading"	11.86	830.2	0

**Since normal clinical investigational employment has evidenced an apparently limitless margin of safety at all dosage levels used, the actual ingestion of gross amounts of the pellets (and rectal "overloading" with them and with the suppositories) was undertaken to demonstrate effects—if any—of aberrant, or perverse, routes of administration, should such be accidentally employed.

† Since the responses (i.e., any observed curarization) were entirely negative as these dosage levels were reached, it was deemed unnecessary to go beyond them.

‡ Represents extrapolation of ** in terms of a hypothesized 70 kg. human.

*Acknowledgment is made to the Department of Pharmacology, Stanford School of Medicine, and Mr. Bing Moy of that department for the dog experiments; work with the other animals was performed by Cugil Laboratories, Inc.

d-tubocurarine and, when administered sublingually, disintegrate in from 20 to 30 minutes.

Curare is almost ineffective when swallowed. This has been explained on the basis of its slow absorption in the alimentary canal and its rapid elimination in the urine. The liver is thought to detoxicate curare. While there is no strong evidence to support detoxication by the liver, the results of sublingual administration lend some support to this theory. The sublingual method does afford a means whereby drugs may in part circumvent the portal circulation. It has been shown by Everett[2] that rats can detoxicate and eliminate curare, independent of liver and kidney function. However, this does not prove—as Everett readily admitted—that liver and kidney function play no part in the destruction and elimination of curare. Mahfouz[6] and Marsh[7] are in accord with this concept. If circumventing the liver is in part responsible for the efficacy of the sublingual administration of curare, then the rectal method should also be satisfactory. Preliminary tests with curare in suppositories indicate that this is true.

Notwithstanding adequate clinical evidence as to the safety of these dosage-forms (and the fact that they elicit only a sub-subjective, infracurarization) it was decided to exert every means—in animal trials—to elicit an objectively discernible degree of curarization (however slight) by resorting to aberrant routes of administration and gross "overloading" with the alkaloid.

As shown in Table 1 maximum actual doses administered to animals were extrapolated in terms of a hypothesized 70 kilogram human. When these actual animal doses reached 27.9 mg. per kilogram of body weight, or a theoretical ingested dose of 1953.0 mg. (651 three-milligram pellets) for the 70 kilogram hypothesized human (at least 78 times a lethal injected aqueous dose of 24 milligrams) further dosage increases were deemed unnecessary in these experiments.

As even with this gross overdosage, there was no observable sign of curarization in any animal, margins of safety for accidentally aberrant, or perverse, self-administration would seem, reasonably, to be without limit.

Success in treating patients with severe painful muscle spasms, who were refractory to both narcotics and mephenesin, encouraged the authors to employ sublingual curare in the treatment of other acute and chronic spastic entities.

A tall athletic male in his thirties, weighing around 250 pounds, had episodes of severe pain in the back and muscle spasm following laminectomy for a herniated intervertebral disc. Opiates afforded only transient and partial relief. Mephenesin did nothing. Sublingual curare effected good relief of muscle spasm and the pain incident to it. As would be expected, the soreness did persist. On one occasion, however, the patient complained of severe pain and "muscle spasm," neither of which was relieved by curare. In fact, a supplemental dose of curare was given intravenously to the point the patient had pronounced diplopia, and yet there was no relief. Physical examination before curare was given had revealed no objective evidence of muscle spasm whatever, but the patient said he felt as though his muscles were in knots. Procaine administered intravenously gave immediate and complete relief. (Curare has no effect on the muscles of the blood vessels, but procaine given intravenously will frequently relieve vasospasm.)

A 16-year-old, 160-pound boy with fracture-dislocation of the neck was completely paralyzed below C-7. Recovery was slow and was complicated by paroxysms of severe and painful muscle spasms in both the lower extremities. Narcotics gave only partial relief of pain, and mephenesin gave no relief of muscle spasm. The episodes of muscle spasm were becoming more frequent and more severe. The neurosurgeon predicted such a train of events, and asked that sublingual curare be tried.

Sublingual curare provided sufficient relief to permit the complete withdrawal of narcotics. Contractions still occurred, but their severity was greatly reduced and they were no longer associated with severe pain. The dose of curare needed to bring this about was 12 mg. four times daily, and sometimes once during the night. The procedure followed was to have the patient place two 2-mg. pellets under his

tongue and repeat at 20-minute intervals until a total of six pellets (12 mg.) had been taken. Orders were given not to swallow or talk during the period of administration.

There was no subjective evidence of weakness in any patient regardless of the dose. It would appear that spastic muscles are much less resistant to curare than are normal muscles and that, in subliminal therapeutic doses, the drug affects only muscles in spasm. When the drug was taken sublingually by the authors in therapeutic dosage (but in the absence of any clinical lesion) no subjective effect whatsoever was noted other than the slightly bitter taste. There was no sign of cumulative action after daily doses ranging from 36 mg. to 54 mg. were taken for one month. In a period of more than a year curare was given sublingually to more than a hundred patients without a single toxic or unpleasant side effect.

Clinical estimation of the effect of sublingual curaré consisted in assessing the power of the patient's hand grip before and after various doses of the drug. Attempts to estimate the content of the drug in the blood plasma after the sublingual administration of d-tubocurarine by the method of Quinn and Woislawski[8] were unsuccessful. This is understandable when it is realized that in their studies, the amounts recovered from the plasma, although small even when an injected paralyzing dose was given, are not determinable below 2 mg. per milliliter by their method. It is apparent, therefore, that the amount of d-tubocurarine present in the blood plasma during sublingual administration is below this level.

Electromyographic studies on a normal subject before and after the sublingual administration of curare were inconclusive.*

A moderate but definite decrease in the power of the hand grip was noted on a dynamometer, although no subjective weakness was felt following the sublingual absorption of curare.

* * * *

During the period of study, the authors gave the drug in the office and observed results within half an hour, since the action of curare is rapid. In fact, it is frequently possible to get results in 10 or 15 minutes. Usually an initial dose of 6 mg. (2 tablets) was given and the patient was observed in 10 minutes. If there was no benefit, another 6 mg. was given. If no improvement occurred within 20 minutes, additional curare was not helpful.

During the study the drug was found not only to be useful as a single, specific therapeutic agent, but also to be of considerable value as an adjunct in therapy. For example, it was frequently quite useful

*These studies are being repeated under controlled conditions on patients with muscular spasm caused by a variety of etiologic factors, by Thomas A. Gonda, Chief of Neurology and Psychiatry Service, Veterans Administration Hospital, San Francisco. This will probably be the subject of a further publication.

TABLE 2.—*Results of administration of curare transmucosally for relief of pain*

	—Degree of Relief—		
BACK PAIN	Good 70-100%	Fair 20-70%	Poor 0-20%
1. Lumbosacral strain:			
a. Traumatic	3	....	1
b. Acute lumbosacral angle	5	1	....
c. Sacralization of L-5	1	....	....
d. Due to pes planus	2	....	....
e. Due to pregnancy	1	....	....
2. Ruptured intervertebral disc	1*	....	3
3. Cervical torticollis	2	3	....
4. Backache due to nervous tension:			
a. Cervical and occipital area	10	1	1
(1) With scalenus anticus syndrome	4	....	....
b. Shoulder and dorsal spine area	1	....	....
c. Lumbar spine area	2	....	....
5. Fracture of cervical spine (old)	....	1	....
6. Backache due to prostatitis	....	....	1
7. Unstable back with muscle spasm	1	....	....
8. Low backache, unknown cause	1	....	....
Total	34	6	6
PAIN DUE TO MUSCLE SPASM IN OTHER AREAS			
1. Traumatic:			
a. Traumatic myositis	2	....	....
b. Traumatic arthritis with surrounding muscle spasm	2	1	....
c. Tear of muscle insertion	....	1	....
d. Muscle strain	1	1	1
2. Cramps:			
a. Leg cramps	4	1	1
b Cramps in buttock following injection	2	....	....
c. Post-encephalitic Parkinsonism with cramps	....	....	1
d. Salt depletion cramps	1	....	....
3. Bursitis:			
a. Deltoid:			
(1) Without calcification	1	....	....
(2) With calcification	2	....	3
b. Olecranon	....	1	1
4. Myositis, non-traumatic	3	1	....
5. Spasm following cerebrovascular accident	2	1	....
Total	20	8	7
ARTHRITIS			
1. Rheumatoid:			
a. Spine	1	1	1
b. Knee	....	....	2
c. Shoulder	....	1	1
2. Osteoarthritis:			
a. Spine	3	1	1
b. Hip	....	....	1
Total	4	3	6
MISCELLANEOUS:			
1. Uterine cramps	....	....	1
2. Extradural hematoma	....	....	1
3. Pleurisy	....	....	1
4. Occipital headache due to abscessed tooth	....	....	1
5. Sciatic neuritis (one case probably due to a ruptured intervertebral disc)	....	....	2
Total	....	....	6
TOTAL OF ALL GROUPS	58	17	25

*This patient had only fair relief of pain in legs.

in relaxing cervical muscle spasm in torticollis due to partial subluxation, prior to neck traction, thus making this maneuver much easier.

Curare is sometimes of value in giving partial relief from pain in the back owing to a ruptured intervertebral disc. However, it will not significantly help the nerve root pain, as would be expected from the nature of its action.

Another valuable use is in treating a scalenus anticus syndrome. It is quite effective in alleviating the symptoms of this syndrome and thus is of diagnostic as well as therapeutic value. In many cases, it is possible to avert the need for severing the muscle by using the drug for a few weeks during the acute phase.

The drug was also found to be of some value in differential diagnosis when used as a therapeutic test, bearing in mind that its action is specifically limited to relieving pain by relaxing muscle spasm. For instance, it is of value in determining whether pain in the neck and back is due to muscle spasm resulting from nervous tension or to organic change as in renal or prostatic disease. In one case, occipital headache was thought to be caused by tension but was not relieved by curare, and ultimately was found to be due to an abscessed tooth. In another case rather obscure pain in the chest did not abate when curare was given and the patient was later found to have pleurisy. Curare is also occasionally of value in differentiating puzzling abdominal pain, since it will relieve pain due to abdominal muscle spasm such as occurs in a rectus tear or strain, but is of no value in treating the smooth muscle spasm of uterine cramps or a bowel lesion. It is also of no value in relieving pain due to tumors, as in the case of a patient with an extradural hemangioma, in which the cause of the pain was at first rather puzzling.

Another interesting observation was that although the drug works best on muscles which are palpably in spasm, it will also frequently give pronounced relief where no muscle spasm can be felt. This was noted particularly in several patients who had had considerable pain from muscle cramps caused by injection of mercuhydrin into the buttocks. These muscle spasms were never palpable, but nevertheless pain did not develop if curare was administered first.

In some cases it is possible to identify each of different types of pain caused by an injury. Several patients, for example, had wrenched knees or bruised extremities or had bursitis. Curare relieved the pain due to the associated muscle spasm or cramps, but the pain due to the bruise itself, or the sprain or bursitis, persisted and could be more accurately localized, and specifically treated if indicated.

In general, the drug was found to be far more effective and reliable than mephenesin. It produced results in many cases where mephenesin had failed. Its action, moreover, is much more prompt, and consequently it is possible to observe the results before permitting the patient to leave the office. Furthermore, the beneficial effect is longer lasting and, in most acute cases, one or two doses are adequate. In cases of chronic pain, one or two doses daily have usually been adequate. The drug has been used in a half dozen such cases for as long as nine months without toxic effects.

Recently the authors have been administering d-tubocurarine by rectal suppository with considerable success in chronic cases. Given in that manner the drug has a slower and more prolonged action, and the method has been very useful, for example, in patients with muscle spasms and contractures following a cerebrovascular accident. A continuation of this means of administration is in progress, with promising results, and will be the subject of a succeeding report.

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Stenosis of the Urethral Meatus in Boys

Surgical Correction

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• Stenosis of the external urethral meatus in boys is not an uncommon developmental defect. It may cause disease higher in the urinary tract and unless corrected may lead to permanent damage.

The most effective treatment is meatotomy, which can be carried out in a physician's office by a method described.

STENOSIS of the external urethral meatus in boys occurs frequently but either is not recognized or, too often, is considered an insignificant developmental defect not requiring medical care. As a cause of chronic urinary tract obstruction, it cannot be ignored. Campbell[2] in a recent review of the subject of hydronephrosis noted that stenosis of the urethral meatus was the etiologic factor in approximately one per cent of cases. A lesion that is so obvious and easily recognized ought not be permitted to persist long enough to cause renal damage.

ETIOLOGY AND PATHOLOGY

Stenosis of the external urethral meatus is a developmental defect. The phallic portion of the male urethra is formed in the embryo in the fourteenth week by a coalescence of the lips of the urethral groove which extends distally to the glans penis. Arey[1] said that an epithelial plate extends distally from the urethral groove into the glans, the plate forms a groove by splitting, and the lips of the groove grow together to form the distal segment of the urethra and the external meatus. (A shallow groove would result in a narrowed distal segment and a stenosed urethral meatus. The characteristic appearance of a stenosed urethral meatus would seem to support the foregoing hypothesis.) A stenosed meatus is situated at the apex of the dome of the glans penis and the opening is round. The normal urethral meatus is oval in shape and extends from the apex of the glans downward to the frenum (Figure 1).

The important pathologic changes associated with stenosis of the external urethral meatus are its effect upon the urethra, bladder and upper urinary tract. Dilation and tortuosity of the urethra result from stenosis of the external meatus. If obstruction continues the bladder musculature eventually becomes trabeculated and decompensation results: The ureterovesical valve does not function and each micturition is accompanied by reflux of urine to the upper tract. The ureters become dilated and the kidneys become hydronephrotic. Ultimately, if the obstruction is not relieved, the renal parenchyma is damaged.

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SYMPTOMS AND DIAGNOSIS

Stenosis of the urethral meatus is not always accompanied by symptoms. A parent may notice a child straining during micturition and may note that the urinary stream is fine or split. The child may complain of dysuria and abdominal pain during and shortly after voiding. Signs and symptoms of infection in the urinary tract manifested by repeated bouts of urinary frequency, dysuria, chills and fever, and pyuria may lead to diagnosis of stenosis. Occasionally enuresis, hematuria and discharge of pus are the symptoms first noted.

Meatitis may be a persistent complication of stenosis of the external urethral meatus. Edema and redness at the meatus or hemorrhage and incrustation may occlude the orifice and the child may complain of severe pain when he urinates. Local and systemic therapy are frequently ineffective. Meatotomy will effect a cure.

In rare instances, hydronephrosis may result from stenosis of the urethral meatus. A careful examination of the urinary tract, including cystoscopy, pyelography and renal function tests should be carried out in any case in which a child has recurrent infection of the urinary tract secondary to stenosis.

To diagnose stenosed external urethral meatus it is necessary only to observe that the meatus is round, of pin-point size and situated at the apex of the dome of the glans penis. There may be no symptoms. Calibration of the orifice is neither necessary nor practical.

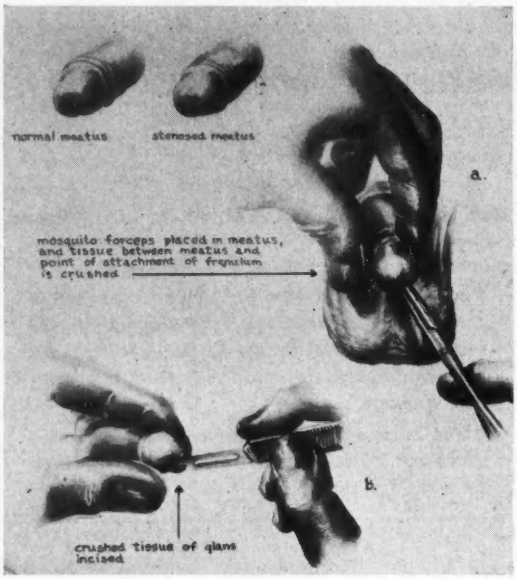

Figure 1.—Operation for correction of stenosis of the external urethral meatus.

TREATMENT

Stenosis of the external urethral meatus is best treated by adequate meatotomy. (In some cases it is possible to enlarge the narrowed opening by inserting sounds or silk woven bougies, but the procedure must be repeated if an adequate orifice is to be maintained, and failure is not uncommon.) Meatotomy may be carried out as an office procedure with local anesthesia brought about by injection of four minims of 2 per cent procaine hydrochloride solution into the glans penis just ventral to the stenosed meatus. One blade of a sharp pointed mosquito hemostat is introduced into the urethra for a distance of 0.5 cm. (Figure 1, a) and then is locked, thereby crushing the tissue between the meatus and the point of attachment of the frenum to the glans penis. The locked forceps are kept in place for six minutes to provide hemostasis (Figure 1, b). A No. 11 Bard-Parker knife blade or scissors may be used to cut the crushed ridge of tissue.

After the operation a small amount of boric acid ophthalmic ointment should be injected once daily into the enlarged urethral opening. This can be done by the patient's parents. Tubes containing the ointment have a long, conical tip that can be inserted easily into the meatus and that acts as a dilator. Two weeks after meatotomy and again three months afterward the meatus should be calibrated by insertion of sounds.

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Primary Cutaneous Coccidioidomycosis

The Criteria for Diagnosis and a Report of a Case

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• *Study was made of a case of coccidioidomycosis known to have resulted from primary inoculation of the organisms into the skin. Clinical observations and laboratory data were obtained at the time of clinical illness and for a period of five years thereafter. From the information thus obtained and correlation of it with what already was known of coccidioidomycosis, it was concluded that the disease originates very rarely as the result of primary cutaneous inoculation. In most instances lesions suspected to be of this type have actually resulted by dissemination of the organisms to the skin from a previously unrecognized pulmonary focus.*

Primary cutaneous coccidioidomycotic lesions closely resemble the primary cutaneous lesions (chancres) in other infectious granulomata, such as syphilis, tuberculosis and sporotrichosis. Spontaneous involution should occur within three months and then there should be immunity to reinfection in all but one or two per thousand instances.

From these observations certain criteria were evolved by which to determine in a case of coccidioidomycosis with cutaneous manifestations whether or not the infecting organism entered through the skin.

IT IS NOW ACCEPTED that coccidioidomycosis usually occurs as a pulmonary infection, resulting from the inhalation of dust containing the arthrospores of Coccidioides immitis. In addition, however, almost all writers on the subject have indicated their belief that in some instances the disease results from primary inoculation of the fungus directly into the skin.[3, 4, 13, 18, 23, 24] In many of the reports recorded in the literature the observers believed that the disease had been acquired in this manner;[1,2,5,6,8,16,19,27] this is true even of the first case ever to be described in North America, that reported first by Rixford[25] in 1894 and again later by Rixford and Gilchrist[26] in 1896, of which it was stated that the initial lesion occurred on the "back of the neck where the collar band rubbed."

The present concept of the pathogenesis of coccidioidomycosis, however, leads to the conclusion that the skin is very rarely the portal of entry. Indeed there is but a single case recorded in the literature (that reported by Guy and Jacob[15] to be referred to later) in which the facts and their chronology reasonably warrant the conclusion that the infection was acquired by this route. The remainder appear almost certainly to represent instances in which a cutaneous lesion, although admittedly the first observed manifestation of the presence of the disease, actually resulted from the dissemination of the organisms to the skin from an earlier, unrecognized, primary pulmonary infection.

The determination of the manner and route of acquisition of the infection is important not only in studying epidemiologic aspects and pathogenesis of coccidioidomycosis, but also it may be of medicolegal importance. Thus, decision as to the justification for compensation of an illness as occupational may be necessary. Also, amputation of a limb or surgical removal of tissue may be wrongly advised in the belief that the "primary" lesion as well as all diseased tissue can thereby be eliminated, when actually the lungs and perhaps other organs are actively involved.

During the past five years the progress of a patient who undoubtedly acquired coccidioidomycosis by direct primary inoculation of the fungus into the skin has been closely observed. The subsequent course of events has strengthened the view that certain criteria can be assigned as necessary for the diagnosis of "primary cutaneous coccidioidomycosis." In the present communication these criteria will be enumerated and their significance discussed.

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TABLE 1.—*Immunological tests* in a patient with primary cutaneous coccidioidomycosis, arranged chronologically*

Duration of Infection	Reaction to Test Material in Various Dilutions					
	Intracutaneous		Precipitin		Complement Fixation	
5 weeks	1:100	+++	Undiluted	++++	Serial dilutions from 1:2 to 1:256, all negative	
	1:1000	++	1:10	++++		
			1:40	++++		
16 weeks	1:100	++++	Undiluted	++++	1:2	++++
	1:1000	+++	1:10	++++	1:4	+
			1:40	Negative	1:8 to 1:256	Negative
30 weeks	1:1000	++++	Negative to all dilutions		1:2	++++
					1:4	+
					1:8 to 1:256	Negative
56 weeks	Not done		Negative to all dilutions		1:2	++++
					1:4	++
					All others negative	
4½ years	1:1000	+++*	Negative to all dilutions		1:2	+++
					All others negative	

*The authors are indebted to Dr. Clement Counter of Long Beach for the performance of some of these tests.

REPORT OF A CASE*

On March 20, 1948, in the course of his regular duties as an employed embalmer, a 32-year-old white man severely abraded the dorsal surface of the proximal phalanx of the right middle finger against a casket. Four days later the area appeared swollen, reddened and mildly tender. The accident was reported to the employer but medical care was not sought until the 16th day after the injury. There was then at the site of the abrasion a mildly tender, deeply indurated granulomatous lesion, 2x1 cm. in size, with a central ulcerative cavity. The hand was moderately swollen and erythematous but neither lymphangitis nor lymphadenopathy was present. The oral temperature was 99.6 degrees F. On April 9 (20th day) the temperature was 101.0 degrees F. in the afternoon. Eight scattered, poorly defined but discrete firm subcutaneous nodules were observed on the dorsal surface of the forearm extending to the elbow. During the succeeding few days the right epitrochlear and axillary glands became enlarged and tender.

Results of routine urinalysis and examination of the blood were within normal limits. The sedimentation rate was 14 mm. in one hour (Westergren method). Tularemia was suspected but smears, cultures and agglutination tests were negative for the organism. In darkfield examination no spirochetes were seen and reactions to serologic tests for syphilis were negative. A roentgenogram of the chest was interpreted as normal. Tests for typhoid and paratyphoid gave negative results. Reaction to a tuberculin patch test was moderately positive. A specimen excised from a nodule for biopsy was interpreted as "non-specific granulation tissue."

The patient first came to the attention of one of the authors (J.W.W.) on April 23 (34th day) for consultation relative to a tentative diagnosis of primary tuberculous complex, which indeed seemed acceptable clinically and was concurred in by Dr. M. E. Obermayer. However, because of the possibility of sporotrichosis (suggested principally by the chain of subcutaneous nodules along the course of the lymphatic vessels), material taken from the primary "chancre" and from one of the subcutaneous nodules was inoculated into Sabouraud's glucose agar. Growth was noted on the third day in all cultures and observed to be inconsistent with Sporotrichum schenckii, but not otherwise identifiable at that time. On the fifth day, however, a few arthrospores suggestive of Coccidioides immitis were seen on microscopic examination of fragments of the culture, and this identification was confirmed the next day. Mice were inoculated intraperitoneally with this culture material, and at autopsy ten days later sporangia (spherules) containing endospores typical of C. immitis were seen. Special attention was then given to a review of the histopathologic section previously referred to and endosporulating spherules were noted.

Immunological tests for coccidioidal infection were carried out, beginning as soon as the diagnosis was suspected and at appropriate intervals thereafter during the course of the illness. The most recent was shortly before the preparation of this report. The results are given in Table 1. The sequence of events is graphically illustrated in Chart 1.

With the diagnosis thus established, further investigation disclosed that shortly after the injury to the patient's hand had occurred he had embalmed the body of a person in whom the cause of death was disseminated coccidioidomycosis. This had been recognized antemortem by those in charge of the case and was so recorded eventually on the death certificate; at autopsy† widespread lesions containing myriads of coccidioidal organisms were noted in the abdominal viscera, skin, lungs and bones. However, neither the patient in the present case nor his employer was aware of these facts at the time the embalming was done. It was also recalled that during the procedure of preparing the body, which entailed considerable handling of the visceral organs, bloody and seropurulent material had entered through a cut in the patient's right glove and had come into contact with the previously injured area.

The patient had not lived in or recently traveled through any of the areas recognized as endemic for coccidioidomycosis and had noted no recent respiratory illness.

The photographs (Figure 1) were unfortunately not obtained until May 5, the 44th day of the illness (dating from the inoculation), at which time the "chancre" had involuted approximately 80 per cent toward normal. It is important to emphasize that this beneficial change had occurred entirely spontaneously, since no specific treatment had been administered. In fact the diagnosis had been established but a few days at that time. The significance of this feature will be discussed later.

The axillary nodes became fluctant on April 26 (37th day) and were incised. From them came purulent fluid in

*Permission to study this case and utilize the experience gained thereby as the basis of this report was cordially granted by Carl Johnson, M.D., of Long Beach. The authors are also indebted to Norman E. Levan, M.D., of Bakersfield for bringing the case to their attention.

† Performed by Edward M. Butt, M.D., Professor of Pathology, University of Southern California School of Medicine.

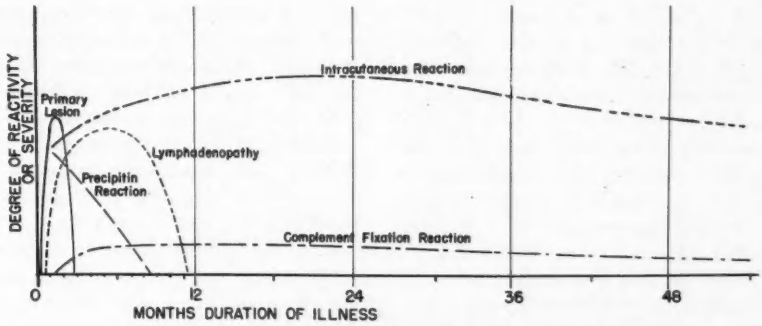

Chart 1.—Graphic representation of the sequence of events in primary cutaneous coccidioidomycosis.

which Coccidioides was demonstrated both by direct microscopic examination and by culture. Moderate numbers of the organism were also noted in histopathologic preparations of a specimen taken from an incised node.

By June 10 (80th day) the original primary "chancre" had entirely healed and the subcutaneous nodules of the forearm had disappeared without ulceration. The fever had subsided and the sedimentation rate was 10 mm. in one hour. As before, results of urinalysis and of routine examination of the blood were within normal limits. The axillary lymph nodes were still swollen but drainage had ceased. The patient returned to work. The residual lymphadenopathy slowly but completely subsided.

The patient has been well during the succeeding four and one-half years. At present a slight scar is visible at the site of the original inoculation and another in the axillary region.

COMMENT

It is noteworthy that in the case here reported the disease resulted from the inoculation of the organism when it was in the "spherule" or "tissue" stage, in contrast to the "arthrospore" or "culture" phase in which it was acquired from dust in all other heretofore reported cases of infection of humans. It may be argued that this case cannot therefore reliably be accepted as prototypical of what can be expected to result from percutaneous inoculation of natural dust containing arthrospores. However, all experience gained in animal inoculation experiments indicates conclusively that no matter which form of the organism is used for inoculation the resulting disease is always identical.

It is obvious that the skin may become involved by coccidioidal infection in two entirely different ways, either by inoculation of the organisms directly into the skin of a previously uninfected person or by dissemination of them to the skin from a primary pulmonary focus of infection acquired some time before by a person whose immunological mechanism fails to focalize the infection. It is the authors' contention that there is much variation between the two cutaneous pathologic processes which follow respectively these two routes of acquisition; they differ significantly in the chronologic sequence of events, in symptoms, in the gross and microscopic pathologic changes they cause, in the manner of extension, in serologic and immunologic manifestations, and in the ultimate prognosis. Each of these subjects needs consideration if the subject is to be adequately covered.

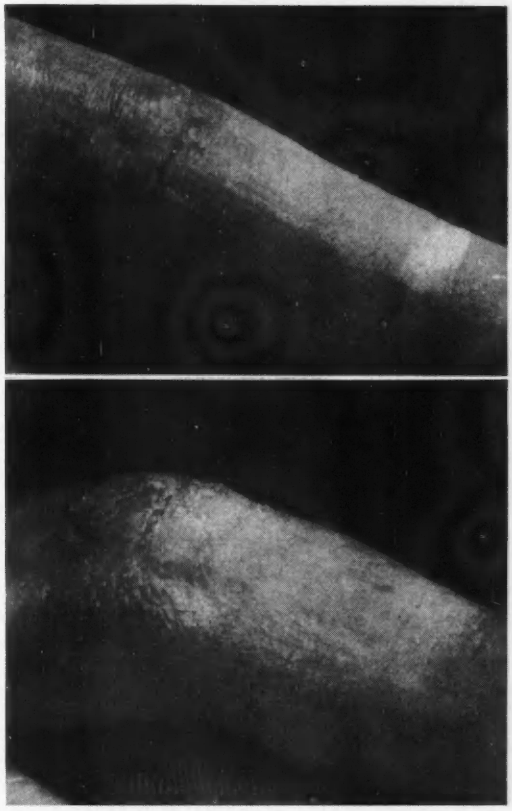

Figure 1.—Primary cutaneous coccidioidomycosis. Lesion on middle finger six weeks after inoculation. *Above*, dorsal view; *below*, lateral view.

Chronology

In the first 42 years after the discovery of coccidioidomycosis, when only the serious, granulomatous form of the disease was recognized, it was natural to conclude that in previously "normal" persons the sudden appearance in or under the skin of a lesion provably due to this fungus indicated that it had been inoculated into the skin directly at that point. This conclusion was even more forcefully supported in cases in which there was known to have been recent trauma at the site, frequently a penetrating wound, which obviously could have been a portal of entry for the pathogenic organisms.

An explanation which more closely adheres to the facts has been available, however, since the discovery by Dickson[9, 10] and Dickson and Gifford in 1937[11] that "San Joaquin Valley Fever" is due to a primary pulmonary coccidioidal infection frequently accompanied by allergic manifestations in the skin consisting of lesions of erythema multiforme or erythema nodosum. In all patients in whom such allergic symptoms develop the prognosis is excellent. In addition, subsequent studies have demonstrated that most of the long-time residents of endemic areas have undergone pulmonary coccidioidal infections, in two-thirds of them in so mild a form as to have been completely inapparent and thus unrecognized. Even though this initial pulmonary invasion remains asymptomatic, however, dissemination to other organs may occur later, and in many cases the first such lesion to be observed will appear in or beneath the skin; indeed, it is now evident that the skin is an organ of predilection in this regard. Also, it is suspected that when dissemination is in progress or imminent, local trauma, whether or not of such a nature as to penetrate the skin, predisposes the injured area to early involvement by the infection.[14, 19, 33] Such cutaneous events as these have been observed repeatedly in patients who were known to have previously acquired coccidioidomycosis by the primary pulmonary route; it seems logical to attribute many less definitive cases to the same mechanism, simply postulating that the preceding pulmonary infection was too mild to have been recognized as such.

To avoid repetition the variations between the two types of infection with regard to the sequence of events will be pointed out in connection with the subject matter covered by the succeeding paragraphs.

Symptomatology

The relative freedom from pain or tenderness in the so-called primary cutaneous "chancre" was a pronounced feature of the process in the case herein reported, as were the firm induration around it, the lymphangitis, the nodules along the lymphatic vessels draining the site, and the regional lymphadenopathy. These observations are all deemed significant.

There is a striking similarity between primary cutaneous coccidioidomycosis (as exemplified in the case reported by Guy and Jacob[15]* and in the present case) and the primary "chancre" phase of several other infectious granulomatous diseases. The syndrome of the mildly painful, deeply indurated, duskily erythematous, ulcerative nodule arising at the inoculated site, followed shortly by regional lymphadenopathy and a moderate constitutional reaction, all having a tendency to subside spontaneously within a few weeks or months, is encountered with but minor variations when the skin has been inoculated with the causative organisms of syphilis, tuberculosis, espundia (American leishmaniasis), sporotrichosis and yaws. In espundia and sporotrichosis there are also commonly tumorous nodules along the regional lymph channels such as were observed in the present case. Aside from this feature, the resemblance to the primary tuberculous complex, when the portal of entry is the skin, is especially close. This is not unexpected when it is recalled how closely coccidioidomycosis mimics tuberculosis in many other phases of pathogenesis, development of symptoms and pathologic changes.[7, 28, 33]

However, the symptoms which result from dissemination of coccidioides to the skin from a previous pulmonary focus are entirely different. Such a lesion begins as an indurated subcutaneous nodule, which then slowly enlarges. At times it develops into a painful abscess which ruptures to the surface and remains for weeks or months as an ulcer or a draining sinus but with little surrounding induration; even more frequently the original blood-borne fungi produce a verrucous plaque with serpiginous, slowly extending borders. There is practically no tendency to spontaneous healing; rather, the skin is likely to become involved over an ever expanding area with a chronic ulcerative, purulent, crusted process. Lymphadenopathy does not ordinarily occur unless bacteria secondarily invade the area.

Pathology

The gross pathologic changes resulting from infections occurring by the pulmonary and by the cutaneous routes have already been described in the preceding paragraphs and the variations between the two entities emphasized.

In histopathologic study of material taken from the original "chancre" in the case herein reported, reaction of mixed type was noted, varying from an acute inflammatory infiltrate in some areas in which polymorphonuclear cells predominated with some eosinophils and lymphocytes, to a chronic, granulomatous reaction in contiguous spots, in which epi-

*It is necessary to point out that in that case secondary coccidioidal lesions developed later beyond the drainage area, suggesting dissemination. The patient recovered, however.

thelioid cells, small lymphocytes and giant cells were seen. With the exception of the eosinophils, these are the histopathologic features commonly considered to be typical of coccidioidomycosis, regardless of the location or type of infection. The coccidioidal spherules were sparsely distributed and difficult to discover. The same pattern was observed in material taken from the regional lymph nodes.

These features are at variance with those to be expected in primary "chancres" of other infectious granulomatous diseases, at least in the early phases wherein an acute reaction predominates and the causative organisms are present in large numbers. It is most important, however, to recall that the tissue examined in the present case was not obtained until five weeks after the onset of the infection, at a time when considerable involution had taken place. In comparison, a "chancre" due to syphilis would have similarly involuted during such an interval so that the original acute phase of the inflammatory process would have become more chronic and the spirochetes much reduced in number. Hence it does not seem warranted to conclude that the histopathologic studies in this case supplied evidence against an intracutaneous portal of entry, although it must be admitted that they did not assist in proving it. It is hoped that when similar cases are encountered in the future, specimens may be obtained for biopsy as early as possible so that this feature may be clarified.

The Significance of the Immunological Tests for Coccidioidal Infection

During recent years extracts prepared from cultures of Coccidioides immitis have been employed in an ever increasing proportion of cases of coccidioidomycosis because of their value as diagnostic and prognostic aids. Three testing procedures have been developed: The so-called "skin test,"[18, 20, 29] in which the reaction to the intracutaneous injection of "coccidioidin" is observed, and two serological tests, one for the demonstration of complement fixation,[22,30,31] and the other for precipitins.[29, 30, 31] It is necessary to mention that a single "batch" of coccidioidin seldom evokes all three of these reactions suitably; accurate standardization and selection must be carried out in each instance before reliable results can be expected.

From the statistical study of the reactions to these tests as observed in thousands of cases, certain facts concerning their chronologic relationship to the progress of the disease have been established.[20,22,29,30,31,32] The application of this knowledge provides additional evidence regarding the portal of entry of the fungus. The significance of each of these tests in this regard is pointed out in the following paragraphs.

Intracutaneous Reaction. The reaction to the intracutaneous injection of coccidioidin is a diagnostic aid analogous to the tuberculin reaction; for this purpose 0.1 ml. of a 1:100 dilution is usually employed. In addition, it may be of value in ascertaining the prognosis[29] during the course of coccidioidomycosis when used in a sort of "quantitation" by ascertaining the degree of response to various dilutions (1:100, 1:10 and undiluted). Clinicians have learned to rely upon a highly positive reaction to a high dilution as indicating good immunologic resistance to the disease; in severe disseminated cases the "titre" is likely to be low or entirely negative. Jacobson,[17] who first applied the intracutaneous test extensively, used 0.3 ml. of undiluted coccidioidin, which indicates the low degree of sensitivity frequently encountered in the severe disseminated infections with which he was dealing exclusively. Thus, if a patient with a cutaneous lesion persistently has no reaction to the intracutaneous test in a dilution of 1:100, it is probable that the lesion is disseminated from a primary pulmonary focus rather than a primary cutaneous infection. Non-reaction to a single cutaneous test might signify only that the infection had occurred too recently for hypersensitivity to have developed.[29] On the other hand a positive reaction might occur if the lesion had arisen by dissemination from a pulmonary focus, provided the patient had developed resistance.

Thus, a positive intracutaneous response gives no clue as to the portal of entry, but persistent nonreaction bespeaks the pulmonary, rather than the cutaneous, route for the primary infection. In the case here reported upon, strong reactivity was noted whenever the intracutaneous test was carried out throughout the course of the disease. It is unfortunate that the test was not done earlier than the fifth week when the reaction was already positive. Undoubtedly, if testing had been started earlier, conversion from negative to positive which must have occurred would have been observed.

Complement Fixation Test. During the past decade the quantitive complement fixation test has proved of practical value in the diagnosis and prognosis of coccidioidomycosis.[22, 30, 31, 32] In general, the more severe the infection, the higher the titer of fixation. Thus, serum from patients with *extensively* disseminating infection usually fixes complement in a dilution greater than 1:16. However, serum from patients with primary pulmonary infection and a *single* extrapulmonary disseminated lesion may fix complement only in low titer. Thus, high-titered fixation of complement in serum, like cutaneous anergy, would be unlikely in a patient with a primary cutaneous infection. Serum of a patient with a primary cutaneous lesion would be expected to have a low titer or per-

haps not fix complement at all. In the present case the titer was only sufficient to be of assistance in diagnosis (Table 1).

The time sequence may supply an additional clue. The ability to react positively to the complement fixation test develops more slowly than to the precipitin test or the intracutaneous injection.[29] Thus, the appearance of a positive complement fixation reaction in high titer early in the course of a cutaneous lesion would constitute evidence against cutaneous primary infection and indicative that it derived by dissemination from an earlier pulmonary infection. Five weeks after the onset of the cutaneous lesion, serum from the patient in the present case did not fix complement. Even when tested at the 16th week, the titer was still very low (slightly positive in a dilution of 1:4). If the immunologic mechanisms of the patient had been sufficiently defective originally to have allowed dissemination to occur from a primary pulmonary focus to the skin, it is more likely that the resulting cutaneous disease would have continued for a longer time, accompanied by a rise in complement fixation titer. On the contrary, the titer never became high and soon began to decline.

Precipitin Test. Precipitins are usually demonstrable in the serum of patients undergoing coccidioidal infection.[30, 31] The titer is not known to have prognostic significance, its principal use being diagnostic. However, the time relationships of the appearance and disappearance of precipitins may give clues as to the recentness of the infection. Precipitins develop before complement-fixing antibodies (although after intradermal sensitivity to coccidioidin) and seldom persist longer than three or four months after infection is acquired. Thus, absence of precipitins in a patient with a recently developed cutaneous lesion proved to be coccidioidal would be likely to indicate dissemination from an earlier pulmonary infection. In the present case, precipitins were strongly present in the first specimen of serum tested (five weeks), had decreased in titer at four months, and when the next test was done at seven months they had vanished. However, precipitins do occasionally persist for a year or so in the serum of a patient with disseminated infection. Therefore, demonstration of precipitins is not conclusive proof that the infection was recently acquired.

Prognosis

Almost all persons who acquire coccidioidomycosis by the primary pulmonary route recover quickly and are thereafter immune to reinfection. Only one or two per thousand, immunologically defective, subsequently have the disease in the disseminated, granulomatous form that often causes death. It would be most unlikely that the disease caused by primary cutaneous inoculation of the organisms would pursue a different course; indeed, since the skin is so highly reactive to the products of the fungus (coccidioidin) in those persons who do acquire immunologic resistance, inoculation by the intracutaneous route theoretically should result in conferring immunity even more quickly and consistently than does pulmonary infection. Since rapid involution of the primary cutaneous chancre and its sequelae should be expected in all but one or two per thousand instances, the continuation of a cutaneous lesion for more than three months should be considered strong evidence against its having arisen by primary cutaneous inoculation.

Criteria for Cutaneous Portal of Entry

Criteria to be met in determining that the skin was the portal in a case of coccidioidomycosis are, in chronological order, as follows:

1. There should be no history of significant pulmonary disease immediately preceding the appearance of the cutaneous lesion.

2. The history should be suggestive of inoculation through a break in the skin at the site of the first cutaneous lesion observed. Simple "injury" such as a bump or bruise should be considered insufficient evidence.

3. Only a short incubation period should elapse, probably between one and three weeks, before a visible cutaneous lesion develops.

4. The primary lesion should resemble a "chancre" as seen in primary syphilis or the primary cutaneous tuberculous complex, rather than an abscess or torpid cutaneous ulcer. The lesion should be a relatively painless, firmly indurated nodule or nodular plaque, with central ulceration.

5. The precipitin reaction to coccidioidin should soon become positive. It should decline somewhat more slowly than if the disease had been present in the lungs for a few antecedent weeks.

6. The response to the intracutaneous injection of coccidioidin should become positive and should increase in sensitivity (1:1000 dilution) unless immunity fails to develop.

7. The complement-fixation reaction should be negative at first, and remain so for several weeks, after which it should be present only in low titer, unless immunity fails to develop.

8. Lymphangitis and lymphadenopathy should develop, but in the region of drainage only. Development of nodules similar to those seen in sporotrichosis may be expected.

9. Spontaneous healing of the "primary" cutaneous syndrome should occur within a few weeks (unless the patient is immunologically defective: This should be anticipated in but one or two per thousand instances).

Criteria for Cutaneous Lesions Arising by Dissemination from the Lungs

The following findings should be regarded as indicative that a cutaneous lesion is not primary but is derived from a previously unrecognized primary pulmonary infection, although it must be emphasized that the absence of these phenomena does not gainsay the possibility:

1. History of an influenzal or other acute respiratory illness (especially if accompanied by pleural pain) a few weeks or months before the appearance of the cutaneous lesion.

2. Persistence of non-reaction to the intracutaneous coccidioidin test with a 1:100 dilution.

3. Positive reaction in high titer to the complement fixation test, especially if observed early in the course of the cutaneous lesion.

4. No precipitins demonstrable if tested between three and five weeks after the appearance of the cutaneous lesion. (This is less significant than the preceding conditions.)

5. No regional lymphadenopathy or inflammatory nodules along lymphatic channels draining the region of the cutaneous lesion, unless secondary bacterial infection is concomitant.

6. Continuance of the cutaneous lesion without involution beyond three months.

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Relationships in Consultation

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• The cause of medicine is advanced by the proper exchange of services between general practitioners and specialists. As a medical group and singly, physicians stand to benefit by strengthening their relationships; and the one to benefit most of all by this combination of services is the patient.

Any physician of integrity admits that it is impossible for one physician to know all there is to know about every medical subject. The establishment of rules of conduct to be followed by those who get together to solve a medical problem will promote the use of advisory practice.

THE METHODS by which clinical problems can be solved in situations requiring the combined efforts of general practitioners and specialists are important not only in the immediate problem of treating the patient but with regard also to freedom in the practice of medicine.

It is gratifying that so many of us in private practice are gathering together to pool ideas and strengthen our relationships. We should not overlook the special significance of doing this, or the necessity for doing it. The dangers of central control of the practice of medicine may be lying dormant at the moment but they are not dead. We know that weak relationships or discord among those in private work are powerful and welcome wedges to those who still seek undesirable controls. Even minor disagreements are immediately magnified to bolster their arguments for government-directed medicine.

Only because it is so constantly true is it trite to say that the chief concern of conscientious practicing physicians is the welfare of their patients. The work we do routinely, the fact that we come together at frequent intervals for discussion, the flow of literature that keeps us abreast of the times, experiment and research directed toward providing the public with the highest grade of medicine we know—all these things offer constant and potent evidence of regard for the individual.

We look, however, for added ways to insure independence in the practice of medicine. We find that certain factors are more conspicuous than others, and are therefore most helpful in making the aims of the group apparent. An excellent example, among several such noticeable factors, is the cooperation manifest in consultation.

STRENGTHENING COOPERATION

Good cooperation in consultation offers one of the strongest proofs to the public that we are capable of managing our own affairs. Progress has been made, but consultation is one phase of medicine in which our relationships can and ought to be strengthened considerably to the benefit of patients and the advantage of physicians mutually and singly. Fortunately, what aids the group in this instance also serves to bring about personal fulfillment.

Taking for granted an awareness of the overall picture, in which what we do and how we do it are under constant observation, we may turn attention to the purely personal elements and benefits inherent in consultation.

The purposes of this communication are to suggest what the chief problems are that still surround advisory practice, to outline some of the workable procedures by which to clarify these problems, and thus to promote effective cooperation between general practitioners and physicians who limit their practice.

The work of the general practitioner has long been considered so vital that he has variously been called the bulwark, rampart, backbone, and cornerstone of American medicine. In many places, he is the sole defensive structure available to safeguard the health of the community.

He offers his services in sparsely populated areas as well as in larger centers. Where territories are big, but the inhabitants scattered, he spreads himself over an amount of ground that appalls urban practitioners. In more thickly populated places, often the number of patients and the variety of diseases he treats are equally staggering. No one minimizes the importance of the physician so well informed about so many things and who is called upon to play many varying roles.

It is a man's privilege to choose work for which he is well suited. What he likes to do, he usually does well. The specialist, thinking along these lines, lim-

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its himself to one branch of medicine. His point of view is that, since he cannot hope to know all about every medical subject, he will learn as much as possible about some one angle that has special appeal. Of some 200,000 practicing physicians in the United States, about 20,000 are certified specialists.

Rather than take sides with the many articles that appear in popular magazines, some extolling the accomplishments of those who specialize and others attempting to prove the greater worth of the family physician, we might better bend our interest to determining how we may use each other's skills to the profit of our patients and ourselves, and to the advance of medicine.

In one recent magazine article, the growing insistence upon consultation by the staffs in first-class institutions was referred to as a new-fangled idea dreamed up by enthusiasts going to unnecessary and absurd lengths with theories on modernizing medical procedures. Actually the idea is anything but new. One does not have to read extensively to learn that specialization is as ancient as the Hippocratic oath, and that evidence of consultation dates as far back as medicine itself.

PURPOSES OF SPECIALIZATION

Anyone in practice has had to face the fact at some time that there is a natural limit to one man's ability. He can scarcely expect to bring every case to a successful conclusion by himself. Nowadays we find practitioners more and more frequently calling for advice along special lines. It is definitely not that they are less able, but that such assistance is more readily available.

England tried to exclude consultation from her national medical program. It was not long before it became apparent that the program was harmfully deficient without it, and the plan was then enlarged to embrace some consultation service.

In most areas of this country, we are fortunate that the referring physician can call upon specialists at will. The question arises: When should he call? When should his services be combined with those of a specialist? (Since specialists already confer freely enough among themselves, this point need not be stressed.)

Perhaps the principal indications for calling in a consultant can be stated briefly by outlining a hypothetical case. For purposes of illustration, it will contain more reasons for advisory counsel than would be found in any one case. Suppose that a desperately ill patient has summoned the family doctor. The nature of the illness makes time an important factor. The physician sees that action must be determined quickly, not only because the situation is desperate, but because the family, filled with fear, expresses a lack of faith in the procedure outlined.

The physician himself may be somewhat puzzled as to the diagnosis, or he might want to have his diagnosis confirmed. He may find it extremely difficult to make a statement to this particular family without someone to support his statement. Something may trouble him regarding the management of the patient, or perhaps he merely wishes to share responsibility. Possibly he is not in doubt about anything, but he may reason that the patient, the family, or both, will feel that more is being done if another opinion is added to his. At any rate one thing is certain. The physician must relieve the general tension mounting over the situation. Consultation is his solution.

If the patient has been hospitalized, there is (in the larger hospitals at least) no question whether there should be consultation if consultation would be of any benefit. In fact hospital rules demand it. The demand is most specific in the fields of obstetrics and gynecology—so specific that it occasionally arouses antagonism on the part of those accustomed to less restraint in unstandardized institutions.

Let us suppose that the hypothetical patient is invalided at home. Once it has been decided that consultation would answer a definite need in the case and the additional opinion is sought by the attending physician, or by the patient or the family or all of them—who is it that takes the initiative in calling in the consultant? By all means the physician should assume the responsibility, and quickly, before anyone else speaks up. If he waits an instant too long, he can complicate his problem beyond remedy. It is not necessary to go into some of the weird reasons which so often prompt a layman's choice. It is enough to say that too often the reasons are completely divorced from the qualifications of the specialist chosen to deal with the particular medical problem.

CHOOSING A CONSULTANT

If a consultant has been named before the attending physician has had a chance to speak, but has not actually been summoned, the physician may have only the embarrassment of asking that the selection be left to him instead. This is not quite as bad as if the consultant had already been called, but it is still troublesome, and should be avoided if possible.

Assuming then, that initially or finally the attending physician has his choice, he must choose a specialist he knows to be competent in the confronting situation. At this time, if extreme urgency does not absolutely preclude it, the attending physician

should prepare all possible information and have it ready for the consultant, so that he may be briefed quickly about the case—even to laboratory reports when possible, or x-ray films that might have some bearing on interpretation of the case.

The attending physician, having summoned the best qualified specialist in the community, may have to make a vigorous attempt to suppress feelings of competition and rivalry, just as one would attempt to eradicate any hampering force.

Presumably, the specialist selected is one who is recognized by others to be qualified as a consultant in his specialty. He is known to keep well informed on his specialty, and he has, in consequence of these facts, built up an excellent reputation for skill. Perhaps he comes in from an adjoining area because a small community has no one available in his field, and repeated calls of this kind have given him great and favorable publicity among laymen as well as his colleagues.

The referring physician can well imagine that those involved will be impressed by the entrance of such a figure into the case. They realize he is there because he knows a great deal about a particular medical problem that is at the moment so vital to them.

It is understandable if the attending physician begins to feel a degree of insecurity as he reviews these points to himself. He does not want to lose prestige, but more particularly he cannot afford to be thought of as inadequate. Many questions enter his mind. If the specialist submits a large bill, will his own, in addition, be resented? If the specialist magnanimously makes an insignificant charge, will his appear too big in light of the fact he sought outside advice? Will the consultant's conduct bother him in the course of the case? All of these thoughts can arise to plague him. It is likely that the question of the consultant's conduct gives him the greatest concern.

DEPORTMENT IN CONSULTATION

The innumerable occasions when consultation has proved to be a successful and thoroughly satisfactory course of action attest that the attending physician's anxieties need have no foundation. There are specific defenses against them when they do arise. The only requirement is that the referring physician and the consultant make themselves aware of a few simple and logical rules of procedure. With a minimum of deliberation, a modus operandi can be set up by which the fears mentioned can be allayed, conflict avoided, and advisory practice given the boost it needs to play its role in better medicine.

Assuming that the family physician's own attitude is completely cooperative, there are certain principles of conduct that, if followed, will make the consulting specialist most acceptable. Primarily the consultant must bear in mind that he is called in to work through the physician in charge. Anyone who remains conscious of this will not be guilty of usurping the stage. The ideal consultant, in fact, will go out of his way to keep the physician in charge very much in the picture. When his part has been accomplished, the consultant will even say a few words to those concerned to show that he intends to leave the patient in the capable hands of his colleague.

During his visits, the consultant's attitude will be warm and friendly. His opinions are best stated slowly and with sufficient deliberation to show respect for the situation. If the prognosis as he sees it is not too bad, he may voice his optimism. If hope is not rationally possible, what he says must have been agreed upon previously with the physician in attendance. He must keep in mind, from beginning to end, that he is only a consultant. If he is in accord with the procedure already in operation, he should say so, and not make minor changes in the routine even though for obvious reasons there is considerable temptation to do so.

Under the most favorable conditions, both physicians will see the patient together, although discussion of the case should definitely take place elsewhere than at the bedside—preferably somewhere outside the room. The consultant should never give an opinion without having seen the patient at all. Certainly the hasty "curbstone" consultation is of little benefit to anyone. In other words, the consultant should be provided with the best possible circumstances for a thorough evaluation of the case. If it happens that he is pressed for a statement without notice when alone with the patient, what the consultant says must be dictated by extreme caution. He will be careful in order to protect himself and to guard against leaving behind him a state of hysteria for the family physician to combat if the news is bad.

Fees, of course, should have been agreed upon before the visit if there are any questions on that score. Unless the situation is exceptional, the range of fees for various services is pretty well known to a referring physician with a little experience. If the specialist has been brought in from some distance, or if for any other reasons the customary charges might not apply, a few direct words should straighten the matter out so that there will be no surprises for anyone concerned.

The attending physician is entitled to the assurance that his consultant will not suggest expensive adjuncts to the program previously outlined without talking the matter over first with his colleague, and that he will not burden the patient with overtreatment to justify his entrance into the case. It is not likely that he could honestly disagree with an entire

routine already being followed. Should he disagree wholly, or partially, he has the obligation of discussing his differences with the referring physician before anything is said to the patient. He would then be free to say that he and the attending doctor had agreed on a new program.

THE CONSULTANT'S WITHDRAWAL

After the consultant has seen the patient, has given his opinion and has conducted himself in good form throughout, he is ready to leave the case. This is the time for a friendly word to show, since his work is done, that the case is once more, and completely, the family physician's unless further developments call for his reappearance.

The factors outlined are the main ones to consider in the interweaving of the medical services. Physicians in general practice will find it helpful to look for the qualities mentioned in choosing consultants. If the consultant deports himself in the manner described, there will be no ground for apprehension on the part of the referring physician. Those who specialize will find that their referred work will increase as they give attention to these points. Above all, if the general practitioner and consultant work as a team, interacting as medical needs dictate, they are creating by this active exchange of services the healthy balance which benefits group and individual, and which does so much to advance the cause of medicine.

2001 Fourth Avenue.

CASE REPORTS

- **Nasal Myiasis Caused by the Primary Screw-Worm, Callitroga Hominivorax (Coquerel)**
- **Surgical Correction of Flexion Deformity of the Cervical Spine**

Nasal Myiasis Caused by the Primary Screw-Worm, Callitroga Hominivorax (Coquerel)

DEANE P. FURMAN, *Ph.D.*, Berkeley

SPECIMENS OF A LARVA which proved to be Callitroga hominivorax were forwarded to the author for identification in 1953. These had been collected in the summer of 1952 from a resident of Lone Pine, Inyo County, who had not been out of the vicinity of his home during the period involved.

REPORT OF A CASE

While the patient was reading in his yard a persistent fly buzzed about his nose. He struck at it several times but it was "like a streak of lightning," as he later described it. The fly disappeared, but shortly thereafter a sense of nasal irritation caused the patient to blow his nose. A fly was discharged. During the next two days he experienced slight nasal discomfort with bleeding from one nostril. A physician who examined him then noted no abnormality, but two days later one side of the patient's face was swollen and inflamed. The nasal passages were irrigated and about 25 maggots were removed. Irrigation was then carried out daily for 11 days and about 200 maggots were removed. The patient then completely recovered.

DISCUSSION

This case, apparently the first verified report of human nasal myiasis in California due to Callitroga hominivorax, is rather similar to one described from Kansas by Herms.[1] In that case, however, the patient died as a result of the attack. As early symptoms may be obscure and the tiny first-stage maggots easily overlooked, the possibility of myiasis during the warm months should be borne in mind.

The primary screw-worm is known as one of the most dangerous myiasis-producing flies of the Americas. The parasite must infest the living tissues of a warm-blooded animal in order to complete its life cycle. Normally the adult female fly is attracted to fresh wounds upon which to oviposit. Within a few hours the eggs hatch and the tiny larvae immediately begin to burrow and feed on living tissue, causing increasingly severe injury as they grow. After about one week the mature maggots drop to the ground and burrow in soil to pupate. Within one week to two months, depending on the temperature, the adult flies emerge from pupation.

From the Department of Entomology and Parasitology, College of Agriculture, University of California.

In the United States the primary screw-worm survives throughout the year normally only in the southernmost parts, mainly in southern Florida and Texas. From these sites the flies migrate or are transported as maggots in infested animals to other parts of the country during the warm seasons. During mild winters the flies may overwinter in areas outside their usual range, as in California. A report by Laake[3] indicated that at least three counties in Southern California were infested throughout the year 1950. In all probability this is not an unusual occurrence.

The fly causes tremendous loss of livestock, since untreated animals frequently die of infestation. As indicated by James,[2] man is also often attacked in infested areas.

Acknowledgment

The author acknowledges with appreciation the cooperation of Mr. Fred L. Jones, assistant game manager of the California Department of Fish and Game, who forwarded the specimens for identification and supplied information regarding the patient, and of Dr. Maurice T. James of the State College of Washington, who verified identification of the specimens.

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Surgical Correction of Flexion Deformity of the Cervical Spine

CHRISTOPHER MASON, *M.D.*, LEWIS COZEN, *M.D.*, and LEO ADELSTEIN, *M.D.*, Los Angeles

SMITH-PETERSEN, LARSON AND AUFRANC[4] in 1945 reported five cases in which flexion of the spine was improved by osteotomy of the lumbar spine. La Chapelle[5] reported a similar case but he performed the correction in two stages. Briggs, Keats and Schlesinger[1] improved the deformity by one-stage osteotomy of the lumbar spine. Jones[2] performed osteotomy of the cervical spine in an unreported case.

In the case herein reported upon the deformity was of the neck, not of the dorsal spine.

REPORT OF A CASE

In 1939 a man, then 30 years of age, first noted pain in the neck. Flexion deformity of the cervical spine developed

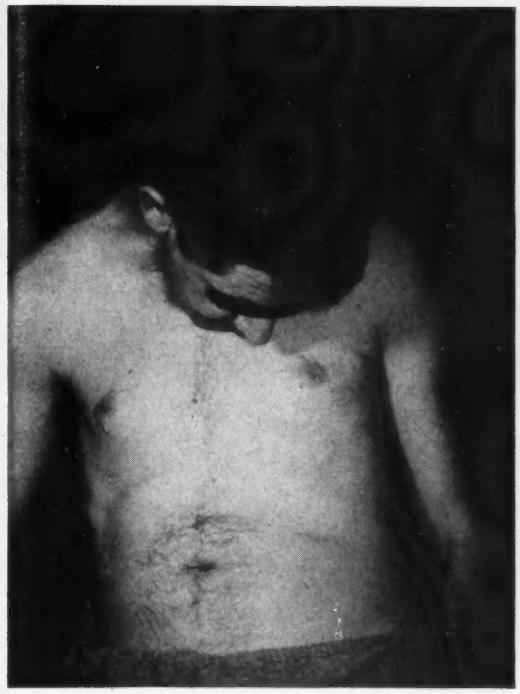

Figure 1.—The patient before operation. The neck was completely rigid in this position.

and became increasingly severe during the next 12 years. The patient was treated intermittently by intramuscular administration of estrone, neck stretching and application of plaster casts, but he did not consistently follow any method of treatment. By 1951 the deformity was severe (Figures 1 and 2). Although the patient was not in pain, he could not see above the level of his legs when walking. He felt moreover that the deformity made him socially unacceptable and was willing to take any risk for correction.

Osteotomy of the spine was carried out. The patient was placed on his side and the back was supported by sandbags. Nitrous oxide was given by inhalation. Intratracheal anesthesia was not possible because of bony ankylosis of the cervical spine. The skin over the cervicodorsal junction was infiltrated with 1 per cent procaine solution and an incision was made in the midline over the spinous processes from C 4 to D 3. The spinous processes at this level were exposed subperiosteally and the spines of D 1 and D 2 were removed with a bone rongeur. The dura and cord were retracted to one side and the body of D 1 was sectioned with a long thin osteotome. The cord was then retracted to the opposite side and the body of D 1 was again sectioned at the same level on the other side. (Apparently the pleura was punctured in the process, for a sucking noise was heard. A tiny hole in the pleura was easily and promptly plugged with a small piece of muscle taken from the adjacent musculature.) The head could now be extended slightly, but removal of more bone in the shape of a wedge was necessary to obtain appreciably more extension.

The wound was closed in layers. Crutchfield tongs were placed in the skull, the patient was placed in bed in a supine position, and 15 pounds of traction was applied to the tongs.

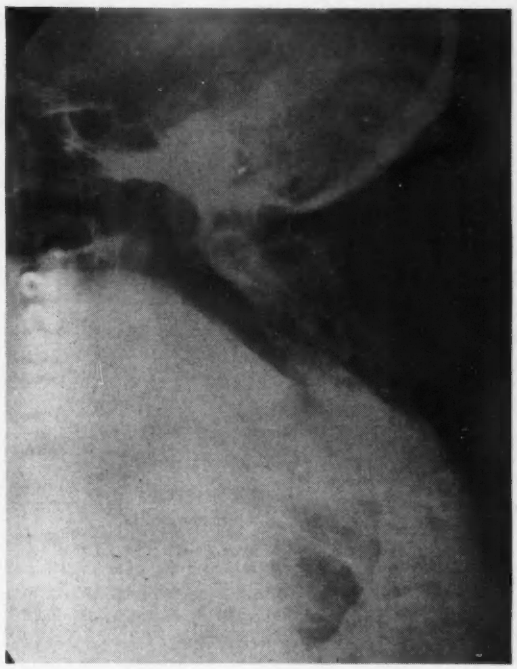

Figure 2.—Lateral view of the cervicodorsal spine before osteotomy.

Figure 3.—Patient soon after operation with neck brace in place.

After two weeks, extension had improved considerably. Hoarseness developed, apparently owing to traction palsy of the recurrent laryngeal nerve. Traction was diminished slightly and the hoarseness immediately disappeared. A plaster of paris jacket extending from head to pelvis was applied four weeks after the operation and the skull tongs were then removed. Three weeks later the jacket was removed and a cervical brace with a head band attached was applied (Figure 3).

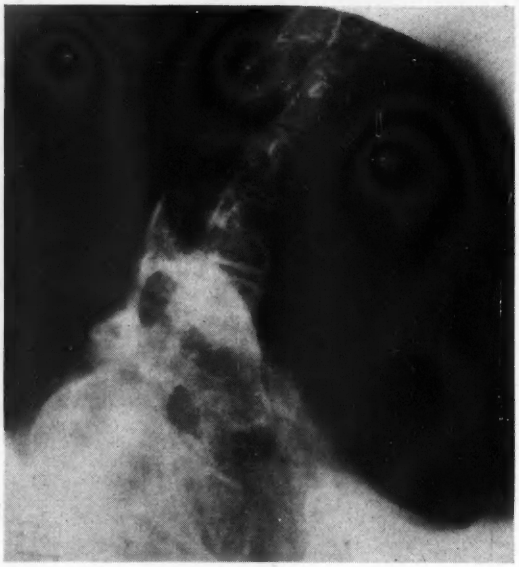

Figure 4.—Lateral view of the cervicodorsal spine seven months after osteotomy. The defect at the level of D 1 appears to be filled in.

COMMENT

Two factors entered into selection of the site of operation in the present case: To avoid injury to the vertebral arteries an area distal to C 7 had to be chosen; and since the apex of maximum deformity was between C 7 and D 2, osteotomy was carried out at D 1.

The only known complication that developed postoperatively was transient recurrent laryngeal paralysis. The patient had foot drop as a result of a previous accident, and although the degree of drop was not measured before operation, apparently the procedure caused no change in it. Nine months after the operation correction was still being maintained (Figure 4).

SUMMARY

A case is reported in which severe flexion deformity of the neck was relieved by osteotomy of the cephalic portion of the dorsal spine.

2007 Wilshire Boulevard.

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California MEDICINE

For information on preparation of manuscript, see advertising page 2

EDITORIAL

Tactful Collection of Overdue Accounts

NO PHASE OF THE patient-physician relationship offers more of a challenge or is more difficult than the problem of patients delinquent in payment of bills for medical services. While some patients are chronic offenders — medical deadbeats — who go from physician to physician and dentist to dentist, never paying any of them, there are others who pose a problem simply because "pay the doctor last" seems to them to be quite orderly.

Persons of the latter sort are of major concern, for they are in most part honest, hardworking and conscientious. They habitually promptly pay the rent and the installments on their cars, TV sets, and refrigerators, yet set aside all medical bills to be paid some time in the future. It is perhaps a compliment—albeit a little wry from the physician's point of view—that they seem to feel the doctor not only can wait but is more willing to do so than other creditors. Not unknown in this order are otherwise upstanding citizens who, even after discussing and making agreeable pecuniary arrangements with a physician, upon restoration to health decide that the fee is too high and refuse to pay.

Physicians have neither time nor inclination to make personal demand for payment from each patient who does not pay. Individual contact by a physician's secretary in a busy office also is much too time-consuming to be practicable. If the delinquent accounts are sent to outside sources for collection, there is risk of losing the good will of the patient not only toward the physician immediately concerned but toward physicians as a group, not to mention the commission that must be paid.

Recognition that tact of the highest order is needed to meet the situation, especially at a time when it seems there is general willingness to hold physicians to blame for all increases in the cost of medical care, has led to the formation of medically-sponsored collection agencies. Under the paternal eye of the American Medical Association, many of the county medical societies throughout the nation have organized a "Bureau of Medical Economics." Here in California, the Alameda-Contra Costa, Santa Clara, San Diego, San Joaquin, Orange and San Francisco county medical societies have pioneered in sponsoring such bureaus. Unique in scope and operation, the bureaus work on a non-profit basis, with each physician who enrolls (at no cost to him) becoming an owner-operator. Overhead is kept to a minimum, and any profit reverts to the members.

In addition to saving money the physician also is secure in the knowledge that the agency representing him in discussions with his patients is acting in accord with the ethics and standards of organized medicine. There is no immediate threat to garnishee wages, to attach cars and personal property, or to resort to any of the many other objectionable commercial practices that cause antagonism and in many cases inflict unwarranted hardship.

Instead, discussions with patients who are not paying money they owe to physicians are carried on in an informal, friendly and sympathetic manner. The reasons for non-payment are explored, overall advice as to budget given when required, and a system of payment arranged which is convenient for the patient. In cases of dire pecuniary distress, recommendations for adjustment of charges are made which invariably are agreeable to the physician and satisfactory to the patient.

It is obvious that the public relations value of this modus operandi, in which a delicate problem is dealt with in a way a physician would like to deal with it himself if he had the time, is incalculable. More widespread utilization of such medically-sponsored projects will do much to remove a source of irritation to physicians and at the same time win new friends for the medical profession.

California MEDICAL ASSOCIATION

NOTICES & REPORTS

The Treatment of Cancer with Arginase

A Report by the Cancer Commission of the California Medical Association

IN THE SUMMER of 1951, inquiries were made of various members of the Cancer Commission of the California Medical Association concerning the usefulness of arginase in the treatment of human cancer. These inquiries were stimulated by the publication of a "Symposium on Arginase in Cancer Research" in a bulletin issued by a medical foundation in California, and by reports emanating from a physician connected with the Hollywood Presbyterian Hospital. The commission conducted an investigation into the nature of the treatment and the results attributed to it.

1. *Nature of Treatment Method*

Arginase is an enzyme which occurs in the liver and other mammalian tissues. It is said to split arginine into urea and ornithin. It is apparently of relatively low concentration in malignant tissue. Attempts have been made for some years to treat cancer with arginase, the drug having been given by various parenteral routes, notably by vein. The question arises from time to time as to the quality and purity of the arginase being used, and as to the possibility of contaminants being the "beneficial" factor, if such exists. The name of the agent was changed by one group to hepasyn in 1953.

2. *Proponents*

The persons prominent in the current arginase discussion are essentially as follows:

Wesley G. Irons, D.D.S., formerly connected with the University of California College of Dentistry.

Ved Vrat, a Hindu biology student, formerly associated with Dr. Irons and subsequently connected temporarily with the Permanente (Kaiser) Foundation.

E. Forrest Boyd, M.D., a Los Angeles physician and surgeon, formerly Chief of Staff at the Hollywood Presbyterian Hospital.

Leo W. Hosford of San Francisco, a drugless practitioner (graduate of the San Francisco College of Drugless Physicians, 1934) and operator of a mortuary college.

Dr. Irons was graduated as a dentist in 1922 and practiced for some years in San Jose. From 1922 to 1943 he worked variously as a student at the University of Southern California, as an anatomist in the Walt Disney Studios, as a director of "research" in the Kern County General Hospital, and reportedly as a shipping clerk and a high school teacher. From 1943 until 1950 he was an instructor in the U. C. College of Dentistry. His interest in cancer reportedly began in 1939 when a relative died of the disease. He apparently became convinced that arginase could control or cure cancer, and proceeded to experiment with it. In 1949, Irons and Vrat were associated briefly. Then Vrat left to join Permanente.

In February 1950, application for a research grant was filed with the Committee on Growth of the National Research Council, from the American Institute of Radiation, in which Dr. W. G. Irons was listed as principal investigator and "Ved Vrat, Histologist" as chief assistant. In August 1950, a letter

that requested withdrawal of the application stated: (1) that Dr. Irons was no longer with the American Institute of Radiation, and (2) that "the Institute is now under the sponsorship of the Permanente Medical Foundation, and has severed all connections with the Electronic Medical Foundation of San Francisco."

Mr. Vrat came to the United States from India in 1946. He entered Stanford but failed to complete the requirements for Ph.D. in the biological sciences. He was disqualified by the University after eight quarters. In 1949 he was a laboratory technician at the Richmond (Calif.) Hospital and in 1950 was listed as Director of Cancer Research at the Permanente Foundation.

In July 1951 Mr. Vrat published three articles indicating control of mouse cancer by arginase in the *Permanente Foundation Medical Bulletin*. Subsequently, Dr. Sidney Garfield, then director of that foundation, asked the Cancer Commission for a list of the names and addresses of physicians in the United States interested in cancer control, in order to send them the *Bulletin*. By October 1951 the rumors concerning a new cancer "cure" reached such proportions that the following letter was released by the Permanente Hospital to the secretary of the Cancer Commission and others:

THE PERMANENTE HOSPITALS
Broadway and MacArthur Blvd.
Oakland 11, California
October 9, 1951

Dear Doctor:

It has come to our attention that there are rumors regarding a claim for cancer cure by the use of arginase and it has been attached to the Permanente Foundation.

We have been working with arginase in the treatment of some mouse transplants of cancer with encouraging results. These results have been published, a copy of which is enclosed. We have used arginase on two patients; one a primary carcinoma of the breast, inoperative, with metastasis to the brain and lung. This patient died during the course of treatment. A second patient with a synovioma of the knee joint, treated by amputation of the leg, but with present widespread metastasis to the lung was treated. To date, this patient has shown no encouraging response to the arginase treatment. These are the only patients that have been treated by any member of the Permanente Hospital or by arginase prepared by our Research Department.

We understand there are other groups, particularly in Southern California, who are using some form of arginase therapy on patients, but we have absolutely no connection either personnel or materialwise with these groups.

I assure you that we have made no claims to cure cancer, as the results of the two patients that we have treated would indicate. Our work is being carefully controlled and we have no intention of publicizing the use of arginase on humans until proper scientific results are obtained. Very truly yours,

THE PERMANENTE HOSPITALS
(signed) C. C. Cutting, M.D., Chief of Staff

In 1953 Vrat treated some leukemic mice supplied by Dr. A. C. Griffin of Stanford and claimed beneficial results. Mimeographed copies of a manuscript bearing his and Dr. Griffin's name were released in the East and caused a flurry of excited speculation. The manuscript was withdrawn at Dr. Griffin's insistence.

In August 1952 Vrat's connection with the Permanente (Kaiser) Foundation was terminated. Dr. Eaton M. MacKay reportedly continued but did not publish further arginase studies.

Dr. Boyd is a Los Angeles physician and surgeon who was graduated from Stanford School of Medicine in 1919.

Mr. Hosford is a drugless practitioner who operates the San Francisco College of Mortuary Science. In 1950, along with Drs. Irons, Boyd and others, he founded the *Charles E. Irons Memorial Cancer Foundation*. This was incorporated on June 4, 1951, and steps were reportedly taken to raise some $135,000.

Mr. Hosford aided Mr. Vrat and Dr. Irons in their arginase work. He notified the dean of one of the medical schools in California that excellent results were being obtained in cancer, using arginase.

On April 21, 1953, Mr. Hosford addressed to the San Francisco, the California, and the American medical associations the following letter:

SAN FRANCISCO COLLEGE OF MORTUARY SCIENCE
America's Premier College
1450 Post Street, San Francisco 9, California
JOrdan 7-0674 and 7-0675
April 21, 1953

Office of the President
DR. L. W. HOSFORD

American Medical Association
535 North Dearborn
Chicago, Illinois

Gentlemen:

We are sponsoring, in collaboration with the Charles E. Irons Memorial Cancer Foundation, a project in basic research with relation to malignancy.

Heretofore, clinical work on humans has been carried on in Los Angeles under the supervision of E. Forrest Boyd, M.D.

We are now setting up an institutional research project at our college at 1450 Post Street, San Francisco, California. We earnestly urge your full and complete cooperation. Should you be interested in this project and in cooperating with us, would you be good enough to advise us, and we will then endeavor to work out arrangements with you as to the nature and extent of your cooperation.

Very truly yours,

SAN FRANCISCO COLLEGE OF MORTUARY SCIENCE
Dr. L. W. Hosford, President

This was acknowledged by the Cancer Commission on April 23, 1953, with a request for information concerning the "institutional research project." No reply was received.

Since the Commission was receiving inquiries

about the cancer treatment project, the secretary of the Commission visited the college on April 30, 1953. He found a small treatment unit, with a few outpatients waiting to be seen by Dr. M. P. Ream of San Leandro. He was informed that Dr. Boyd visited the unit only on Tuesdays or Wednesdays. There were no bed patients. In one room was a gynecological table, without any visible examining instruments or linen. No nurses were visible. A full report of the visit is available in the files of the Commission.

While Dr. Hosford wrote to the medical associations on College of Mortuary Science letterhead, he addressed a prospective patient on Memorial Foundation paper as follows:

President-Research Director
WESLEY G. IRONS,
D.D.S., A.B., M.A., M.S.

Secretary-General Manager
LEO W. HOSFORD, D.P.M.

Vice-President-Medical Director
E. FORREST BOYD,
A.B., M.D., F.I.C.S.

Treasurer-General Counsel
UGENE U.BLALOCK, A.B., J.D.

CHARLES E. IRONS MEMORIAL CANCER FOUNDATION
April 14, 1953

Directors
Wesley G. Irons,
D.D.S., A.B., M.A., M.S.
E. Forrest Boyd,
A.B., M.D., F.I.C.S.
Leo W. Hosford, D.P.M.
Ugene U. Blalock, A.B., J.D.
George E. Chapman, M.D.
George H. Hauerken, LL.B., LL.M.
Leon S. Utter
Edward M. Elliott
J. L. Cannon

Principal Office
1450 Post Street
San Francisco 9, California

Branch Office
727 W. Seventh Street
Los Angeles 17, California

Miss C.
Grandview Boulevard
Los Angeles 34, California

Dear Miss C.:

At last we are able to announce the opening date of our new cancer research treating center in San Francisco, which will be the central point of research of our organization.

The date will be Monday, April 27th, at 1450 Post Street, which is the college building of the San Francisco College of Mortuary Science, the institution under whose auspices this project has been made possible.

Doctor Irons, Doctor Boyd and myself will all be in New York the latter part of this week for a few days and will return to get the treatment started as above stated, on April 27th.

Would you please write me by return mail letting us know if you are still interested in taking these treatments. Would you also see that all of your records together with their biopsies, x-ray reports, etc., etc., are referred to E. Forrest Boyd, M.D., Supervisor, Research Center, 1450 Post Street, San Francisco 9, California. Please do this immediately so we can know how many will arrive and have all applications for treatment in well in advance so there can be no delay in carrying out the program. Doctor Boyd, as stated, will be the Medical Supervisor, and is a man with whom you are all acquainted.

Looking forward to seeing you and your mother on the above date, and hearing from you at the earliest date possible, I am,

Sincerely yours,

DR. L. W. HOSFORD
General Manager

3. *Experimental Evidence Offered*

No formal experimental evidence was offered to the Cancer Commission by the proponents of arginase in 1951. However, a paper reporting some experimental work was subsequently published by Drs. Irons and Boyd in *Arizona Medicine*. This paper quoted a 1946 publication of Irons (*Journal of Dental Research*, 25:497) dealing with subcutaneous and intraperitoneal injection of arginase prepared from fresh beef liver and the reactions thereto in twenty Hamilton-strain white mice. It also quoted a 1947 paper by Irons and Wiswell (Science, 106: 2756) reporting some tests on C_3H cancer-strain mice. A number of mice with "spontaneous mammary carcinomata" were injected with arginase: "The tumors shrank; differential staining methods (Von Kossa) for calcium were positive."

One animal was given arginase daily for three days. "Five days later when the tumor was removed, decalcification was necessary before this mass could be sectioned for microscopic examination."

One animal was given arginase directly into the mesial half of the tumor. After three days "histological examination showed the distal portion to be typically malignant, while the proximal half presented a picture of innocence."

The authors concluded that direct intratumoral injection of arginase produced effects identical with intraperitoneal administration—namely, a 28 per cent reduction in general tumor growth, and a 26 per cent decrease in the ratio of tumor length to weight.

4. *Clinical Evidence Offered*

At the request of the Cancer Commission, and by invitation of Dr. E. F. Boyd, Dr. Ian Macdonald was present at a demonstration of clinical results presented to the Cancer Committee of the Hollywood Presbyterian Hospital on February 20, 1952. Two groups of patients were discussed. The first ten had been observed by a subcommittee of the cancer committee of the hospital; the second ten were cases chosen by Dr. Boyd as being perhaps more representative of results.

Case histories were presented as follows:

(1) Mrs. G., an 88-year-old woman with a breast tumor since 1949. When first seen by the Tumor Board the left breast was completely infiltrated, with ulceration of the skin; there were bilateral axillary and left supraclavicular nodes. Treatment with arginase began on Aug. 6, 1951. Fifty-nine treatments were given. The patient died on Oct. 6, 1951. The pathologist, Dr. Andrews, stated that the original biopsy showed a well-differentiated carcinoma, and that the same neoplasm was seen in sections from the autopsy, with areas of necrosis and fibrosis. The was *no difference* in the pre- and post-treatment microscopic sections.

(2) Mr. H., a 62-year-old male with bronchogenic carcinoma proven by biopsy on July 19, 1951. He had dyspnea, weakness and cough; pleural fluid was aspirated but showed

no cancer cells on smear. Treatment began on July 13, 1951, a total of 50 treatments with arginase was given and the patient died on September 9, 1951. Dr. Benz [radiologist] reported that the major portion of the left side of the chest was opaque, that there was a posteriorly placed mass and there was an osteolytic metastasis to the left scapula. Mrs. Hilliard [laboratory technician] reported that the antienzyme values indicated a rapid process and that the antichymotrypsin rose steadily under treatment.*

(3) Mr. M., a 37-year-old male with a history of two to three years of diarrhea. On Aug. 24, 1950, a colon resection was done for carcinoma of the sigmoid, at which time metastases to the liver were present. In January 1951 he had pain along the left costal margin and in the left shoulder and by May 1951 had lost 40 pounds in weight. On July 20, 1951, there was a large lower abdominal mass and treatment with arginase was begun. By Aug. 3, 1951, there were no changes in physical findings but the patient was undergoing progressive deterioration and died on Aug. 21, 1951. Dr. Andrews reported that the surgical specimen showed a fairly well differentiated adenocarcinoma and that a biopsy of the liver showed the same neoplasm. At autopsy the carcinoma was still well differentiated, there was fibrosis and degenerative change. Dr. Benz stated that a gastrointestinal series showed gastrocolic and enterocolic fistulae. Mrs. Hilliard reported that 33 determinations of antienzymes in blood serum were done and 23 determinations of urinary uropepsins with no evidence of improvement in the pattern at any time. The later findings indicated good adrenal function at first which became worse after treatment began.

(4) Mr. M., a 46-year-old male. In January 1949 developed a lump in the right knee which became larger and was biopsied in June 1949 and showed a fibrosarcoma. On July 25, 1951, the primary lesion measured 9 x 9 x 5 cm. Sixty-seven treatments with arginase were given and the mass was thought to be possibly smaller and softer. The patient had metastases to regional nodes and lungs. Amputation was done. Dr. Andrews stated that the original biopsy showed an active fibrosarcoma with many mitotic figures. The amputation specimen showed necrosis of the tumor with no mitotic figures. There was a collagen increase. Dr. Boyd reports that the patient now has considerable weakness and a cough. He has had no treatment since December 1951. Dr. Benz demonstrated bilateral pulmonary metastases and six weeks after treatment began all of the metastases were increased in size. Mrs. Hilliard reported that the antienzyme pattern showed no improvement.

(5) Mrs. V., a woman with age not given. Developed swelling and retraction of the nipple in January 1950 and an increasing mass in the breast. In December 1950 there were multiple involved nodes in the left axilla. The patient had weakness and pain in the back. Ninety-six treatments with arginase have been given since July 19, 1951, at which time the left breast contained a 6 x 8 cm. central tumor, and there were multiple enlarged hard fixed nodes in the left axilla. Biopsy on Aug. 29, 1951, showed metastatic adenocarcinoma. Last examination on Feb. 19, 1952: The primary lesion of the breast measured 8 cm. in diameter, there was a left axillary mass 3 x 3 cm., the liver edge was hard and irregular and there was a hard mass occupying the umbilicus. This patient stated that she "feels no better." Dr. Andrews stated that the lesion was a well-differentiated adenocarcinoma with fibrosis and no mitoses. Dr. Benz reported that the chest showed pulmonary fibrosis with no evidence of metastases. Mrs. Hilliard reported that the antichymotrypsin fell from 6.5 before treatment to 5.0 in October but by November had risen unfavorably to 8.5.

(6) Mrs. E., a 40-year-old woman. In May 1950, noted a tumor in the breast which subsequently was treated with Koch serum, testosterone and Premarin® with gradual increase in size of the breast tumor. On November 14, 1951, the breast was small, hard and fixed to the chest wall; there was involvement of the axillary nodes on the right side and bilateral supraclavicular node involvement. A biopsy showed scirrhous carcinoma. This patient had 121 treatments with arginase and last examination on Feb. 18, 1952, showed that the mass in the breast was larger, with more skin involvement, and moderate increase in involvement in the axillary nodes which were now fixed to the scapula. She had gained weight. Dr. Andrews stated that he had no microscopic section to review. Dr. Benz said that radiographic examination showed no evidence of metastases. Mrs. Hilliard reported that six determinations had been done. The last one on Dec. 18, 1951, showed unfavorable progress.

(7) Mr. X., a male, aged 56, name not available. In December 1950, nephrectomy was done for a carcinoma of the renal cortex. In June 1951, fractured the right forearm and complained of pain in the back with demonstration of metastases and x-ray treatment to both areas. This patient had had 68 treatments with arginase although the date of beginning such treatment was not stated. At last examination, Feb. 19, 1952, the patient said he felt better but he had severe anemia, was more emaciated, weaker and dyspneic. There was a mass in the right side of the abdomen with induration of the entire abdominal wall. Dr. Andrews reported that slides made elsewhere were typical of a clear cell carcinoma with areas of degeneration and hemorrhage. Dr. Benz demonstrated pyelographic studies done elsewhere with a mass at the lower pole of one kidney. In October there was radiographic evidence of metastases to the ribs and lungs and the last examination in February 1952 showed a mass of pleural effusion filling the entire right side of the chest, extensive destruction of ribs, new pulmonary lesions and a pathological fracture of one radius. Mrs. Hilliard reported that ten tests had been done from November through December showing a moderately progressive pattern, and no essential change.

(8) Mrs. B., a 50-year-old woman. From 1929 to 1930 she had x-ray treatment to her leg for removal of hair. In 1942 she injured her patella and an ulcer developed in this area which became larger and then improved but did not heal. In 1947 a "cyst" of the patella was removed which on microscopic examination showed epidermoid carcinoma. A graft was used for closure. From 1947 to 1951 the patient was well until she suffered another injury to the leg with new ulceration and pain for which a sympathectomy was done. When seen on Nov. 26, 1951, the right leg showed an indolent granular ulcer at the site of the previous operation and on Dec. 18, 1951, biopsy showed epidermoid carcinoma Grade I to II. Since the above time she had been on treatment with arginase, number of treatments not stated. The patient was presented to the group on Feb. 20, 1952, and on questioning said that she felt better. There were three areas of ulceration 2½ x 1¼ inches and 1 inch and ½ inch respectively in size and the base of these ulcers was reported as being "thicker." Dr. Andrews reported the original biopsy and said that there had been no additional biopsy. Dr. Benz reported that radiographic studies showed no change.

(9) A 32-year-old male, name not obtained. In March of 1950 a tumor in the right axilla was biopsied and showed

*Dr. Philip West and Mrs. Hilliard reported on the response of patients by means of the antichymotrypsin and antirennin values of blood serum.

metastatic carcinoma, primary site undetermined. Eight x-ray treatments were given at the Los Angeles Tumor Institute. In February 1951 there was recurrence of the axillary lesion with pain in the shoulder. In May 1951, further x-ray treatment was given. In November 1951 pain recurred with diffuse rales in the lungs and winging of the right scapula. Thirty-two treatments with arginase were given and the patient died one month after beginning treatments. Dr. Andrews reported that autopsy showed a primary carcinoma of the ileum with metastases to the brain and death from cerebral hemorrhage. The microscopic section showed no evidence of change from the treatment given. Dr. Benz reported radiographic findings of hilar adenopathy and miliary pulmonary metastases, which grew progressively.

(10) Mrs. W., a woman, aged 57. In November 1950 a lump in the breast was found and in January 1951, biopsy showed cancer. The lesion, however, was in the underlying chest wall and she went to the Mayo Clinic where some surgical procedure was done and ten x-ray treatments were given and some months later four x-ray treatments were given. The excised material showed chondrosarcoma. Treatment with arginase began on Aug. 12, 1951, and 198 treatments were given. Examination on Feb. 19, 1952, showed around the inframammary scar several soft small nodules; the fourth rib was thickened and stony hard. There was also a chondrocostal mass in the area of the seventh rib. At this point it was learned that on Feb. 1, 1952, the patient had a resection of the chest wall by Dr. Bert Cotton but the disease was so extensive that residual tumor was left attached to the pericardium. Dr. Andrews reported that comparison of the original sections from the Mayo Clinic with the surgical specimen of Feb. 1, 1952, showed definite changes following treatment with arginase, consisting of increase in fibrous tissue with degeneration of cartilage and encapsulation of the tumor.

Dr. Boyd then announced that the present review of his project was being done over his protest, and the reasons for protest were: (1) inadequate time had elapsed to permit proper evaluation; (2) the dose of arginase had not been established as he now gives 20 times greater dosage than at the beginning of the project; (3) an attempt at evaluation on the basis of inadequate evidence is unscientific. He said on the other hand if present review was for a guide as to future conduct of the project, that was satisfactory. He stated that, for the benefit of the representative of the Cancer Commission, the choice of the ten cases supervised by the committee at the Hollywood Hospital was their own and not his. Three of these cases he said fell short of one of the criteria, that they failed to survive for six months after the beginning of treatment. A fourth case he stated was an unfair selection. Concerning Case No. 5 listed above, he thinks there is little difference between the patient's condition now and before treatment. Case No. 6 he thinks should be discarded although he gave no reason for this belief. Dr. Boyd stated that in all over 8,000 doses of arginase given intravenously there had been no death due to the use of the drug in a total of 125 cases. He said that arginase reduces the amount of narcotic the patients require, that they are happier, that some of them gain weight, and that 20 of the patients he has treated have returned to their full-time occupations. He stated that Case No. 10 above was pronounced by the Mayo Clinic to be inoperable, and that arginase made the lesion operable. He said that live patients are all that count and one should see the patients to be convinced of the value of the treatment. Patient No. 10 listed above then was brought in. She embraced Dr. Boyd affectionately and stated that she felt wonderful.

(11) Dr. Boyd then showed a Mrs. N. who had metastases to the left lung from a carcinoma of the breast as demonstrated on Jan. 5, 1950. On April 28, 1950, there was radiographic evidence of lymphogenous involvement of the lung and by June 6, 1951 the left lung was completely obscured. This patient had x-ray treatments in February, March and June 1951 and also had testosterone during these months. Dr. Boyd did not say how much arginase this patient had had or when the treatment began. On Oct. 13, 1951, Dr. Benz showed films with extensive changes in the left lung which he interpreted as being postradiation, as x-ray treatment had been given to the entire left side of the chest. The radiographic appearance in January 1952 was static. Dr. Boyd claimed credit for arginase that this patient was well and had been back at work for ten months.

(12) A child was then shown who at 18 months of age in May 1950 developed epileptic seizures, and was admitted to Children's Hospital in January 1951. Exploration showed a glioastrocytoma of the third ventricle, a biopsy being done at that time. The child had been under treatment with arginase since May 14, 1951, still had seizures and when shown to the group had severe strabismus, was unable to walk a straight line; and it was stated that at home the child was equipped with a small football helmet to prevent injury to the head because of her constantly walking into walls and objects in the room. Dr. Boyd stated that since treatment with arginase the child's "word power" had improved. It was then learned that following the exploration the child received x-ray therapy given by Dr. Robert Freeman in Pasadena.

(13) A child about age three (J.R.) on Sept. 7, 1951, showed a lump on the back of the head which was biopsied and showed fibrosarcoma. Films in Sept. 1951 showed an osseous defect in the occipital bone from without, a sharply demarcated area. The soft tissue tumor was surgically resected, after which treatment with arginase was given. Films taken in January and February showed progressive healing of the former bone defect so that now it is completely bridged by callus. Dr. Benz interpreted these radiographic findings in the skull as being most likely due to pressure erosion of the overlying tumor with an aseptic osteomyelitis. Dr. Boyd maintained that the bone was destroyed and that healing was due to arginase.

(14) A 59-year-old male (Mr. R.) had an adenocarcinoma of the lung proven by bronchoscopic biopsy in October 1951. He was dyspneic and it was difficult for him to talk when treatment was begun with arginase in October, since which time 112 treatments had been given. The patient was shown to the group. He said he still had some cough and had nausea from the medicine which he received but no longer had bloody sputum. Radiographic findings on June 12, 1950, and Nov. 2, 1950, showed a slowly growing lesion at the right hilum, on Jan. 2, 1951, atelectasis of the right upper lobe, on Oct. 25, 1951, extensive involvement of the right lower half of the lung. Further x-ray examination on Jan. 15, 1952, showed a right pneumothorax following an exploratory operation at Sawtelle, while on Feb. 18, 1952, the entire right side of the chest was completely dense.

(15) A woman, Mrs. S., age not given, developed abnormal uterine bleeding in 1948, and was treated by surgery and irradiation at intervals up to 1951 for metastases invading the pelvis from a primary adenocarcinoma of the uterine cervix. Gastrointestinal x-ray examination on Feb. 5, 1952, showed a partial small bowel obstruction and the presence of a lower abdominal mass. Prior to this time the patient had had 100 treatments with arginase and Dr. Boyd stated that the perineal floor which was tight had now be-

come relaxed. At surgery on Feb. 12, 1952, the right half of the colon and some of the ileum was resected. Pathological examination showed the specimen to consist of a mass of loops of bowel bound together by dense fibrosis with a few small foci of cancer cells stated by Dr. Andrews to be present. Mrs. Hilliard reported that this patient was always in positive nitrogen balance.

(16) A Mrs. S., who had an adenocarcinoma of the right breast and radiographic examination Nov. 29, 1951, showed bilateral pleural effusion with nodular densities in the left pulmonary field. On Feb. 18, 1952, effusion was less and there were areas of patchy atelectasis. This woman's original treatment was on Feb. 20, 1951, when she had a right radical mastectomy and this was followed by postoperative x-ray therapy. On five occasions pleural fluid had been aspirated but no smears were obtained. She had severe dyspnea at the time the abnormal radiographic findings were demonstrated and Dr. Brown (radiologist) indicated his belief that the findings at that time were more consistent with cardiac failure than with metastatic disease.

(17) A 33-year-old woman (Mrs. S.) had a squamous cell carcinoma of the uterine cervix for which irradiation was given in February 1949, at the Hollywood Hospital. Following this she was stated to have an abdominal mass. On Feb. 6, 1951, treatment with arginase was begun and Dr. Boyd stated that the patient was now perfectly normal, and it was possible now to do a pelvic examination whereas this was not possible before arginase was given. Dr. Brown stated that the lesion was treated with 7,000 milligram-hours of radium and that x-ray treatment was given from Aug. 29 to Oct. 25, 1949, and from December to January 1950, there was a depth dose of 8,000 r in the midpelvis and 4,000 r in the perimetria. On Jan. 13, 1950, examination by Dr. George Sharp showed no evidence of disease.

(18) A male, age and name not obtained, on March 10, 1951, had a pneumonectomy at Sawtelle for a squamous cell bronchogenic carcinoma in the left lower lobe with infiltration of the pulmonary vein. On May 14, 1951, he began arginase treatment and he was said to have gained 40 pounds in weight and to be working regularly although he had a chronic cough. Serial radiographic examinations were reported from Sawtelle as showing no change since the operative procedure.

(19) A women with carcinoma of the cervix, name and age not obtained, with spread to retroperitoneal nodes, had exploratory operation elsewhere and was brought to Hollywood Hospital by ambulance. The onset of her disease was in February 1950 with uterine hemorrhage, and on July 6, 1951, she was explored and said to be inoperable. Then Dr. Boyd stated that the microscopic diagnosis was leiomyosarcoma of the uterus with abdominal spread. Before beginning treatment with arginase she had had two abdominal masses; she now had three and she would soon be eligible for surgical treatment.

Dr. Boyd then summarized his ideas by saying that arginase had prolonged the lives of 40 patients long beyond their natural expectancy, that 21 of them are back at work, that there has been no damage in any instance, and that some inoperable cancers have been converted to operable. He said that if his premise is correct new vistas are being pioneered. Radiographic findings must be interpreted in an entirely new light (as in cancer of the lung which may seem to be growing denser under treatment, due to fibrosis and deposit of calcium in the tumor with arginase).

He also stated that this treatment opens a new field in microscopy and that new methods of staining and study of tissue are necessary to interpret properly the changes in cancer produced by arginase.

Surgery has an entirely new future in the treatment of cancer, he said, as more than 50 to 75 per cent of cancers can be made operable, he said, by treatment with arginase. Dr. Boyd stated he had a number of patients then waiting for operation who have been made operable by treatment with arginase.

The internist also has a new vista in the field of cancer, Dr. Boyd said, with different symptoms to be interpreted in the light of this new treatment with the necessity of supporting adrenal function along with the use of arginase. He mentioned that insulin does not cure all diabetics.

Dr. Boyd stated that four years of work and a vast amount of money are required. The patients so far treated have spent more than $150,000 at the Hollywood Hospital. Cutter Laboratories, he said, had signed to pursue the investigation of arginase and had assigned a full-time research man to begin work at the Hollywood Hospital in the week of Feb. 25, 1952. [Cutter Laboratories later withdrew. See later paragraph: 9. *Consultant and Other Reports.*]

(20) Dr. Rusche was then asked by Dr. Boyd to describe a case of his, and Dr. Rusche stated that the man had carcinoma of the bladder which after treatment was less vascular, but that there was now extensive spread of tumor posterior to the bladder.

This concluded the session.

5. *Autopsy Data Offered*

The proponents offered no autopsy data to substantiate statements that arginase had verifiable effects on cancer in terms of convincing tissue changes or tumor arrest.

6. *Experimental Evidence Developed by the Cancer Commission and Independent Investigators*

Immediately after the publication of the "Symposium on Arginase in Cancer Research" referred to in the introduction, the Cancer Commission made extended efforts to secure some arginase for research purposes. Some of the drug was promised but none was forthcoming for several weeks. Finally, through the kind services of Dr. Cecil Cutting, Mr. Vrat made available sufficient arginase for Dr. Winsor Cutting to treat two mice that had cancer. The mice died of cancer. Subsequently Dr. Cutting checked the findings on 30 animals, with similar results.

Dr. A. C. Griffin, associate professor of biochemistry, Stanford University, informed the secretary of the Commision on September 24, 1952, that he had completed three series of studies of the effect of arginase on leukemic mice. He wrote: "Right now, I am of the opinion that this drug has little effect on the course of the leukemia with which we are working."

Dr. M. B. Shimkin reported in 1951 that Dr. David Greenberg, professor of biochemistry at the University of California and one of the world's outstanding authorities on arginase, could not confirm shrinkage of tumors in experimental animals with cancer. The animals died of cancer in the usual manner.

Dr. C. C. Stock, chief, Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research (Memorial Center for Cancer, New York City) conducted a series of tests in conjunction with Dr. Irons in 1953, injecting groups of cancer-bearing animals (C_3H/ba mammary adenocarcinoma in C_3H mice) with arginase supplied by Dr. Irons. No significant inhibition in growth and no tumor regression was observed. (Letter to Cancer Commission, June 15, 1953.)

7. *Clinical Evidence Developed by the Cancer Commission*

On January 17, 1952, a subcommittee of the Commission (chairman, Dr. Ian Macdonald) addressed a formal request to Dr. E. F. Boyd to review his work with arginase in the treatment of patients with cancer. This request resulted in the meeting above referred to.

Since that time the Commission has attempted to maintain a follow-up of the cases, with little cooperation from the proponents. Of the original 20 patients discussed at the Hollywood Hospital meeting, three were already dead of cancer at the time of the meeting; three are known to have subsequently died of cancer (cases 4, 9, and 16). Two, apparently well (cases 8 and 13), had surgical removal of the lesion. One had no evidence of disease when arginase was given (case 17). In the remainder there was no objective evidence of improvement.

Members of the Commission have reviewed the following cases or case histories:

(21) Male, child with "sarcoma of the pleura." Treated by Dr. Boyd in Los Angeles in 1952 and x-ray films interpreted as showing calcification of the tumor after three weeks' treatment. Died, within some weeks' time with disease uncontrolled.

(22) Female, with carcinoma of the breast treated by Dr. Ream in Alameda County. Died with extensive metastasis (autopsy).

(23) Male with carcinoma of the rectum. Treated by Dr. Ream. Died with extensive persistent tumor (limited autopsy).

(24) Male, said to have adenocarcinoma of the scalp, metastatic from the intestinal tract. Treated with arginase and lesion "arrested." Subsequent abdominal laparotomy for bleeding peptic ulcer. No carcinoma of bowel found. No verified primary tumor.

(25) Male with operable carcinoma of rectum seen in consultation by Dr. Phillips Johnson. Treated with arginase; tumor became larger. Patient finally agreed to exploration and resection. At time of operation metastases were found in liver.

(26) Female, with carcinoma of rectum, seen by Dr. Robert Scarborough in consultation. Patient had been given arginase by her family physician in 1950 and 1951 and had been told the tumor was "shrunk to fibrous lumps." Upon exploration in October 1951, very extensive inoperable carcinoma was found. The patient died in May 1952 after considerable distress. The sections were reviewed by Dr. David Wood, pathologist, and reported as typical of adenocarcinoma without any evidence of specific arginase effect.

The files of the Hollywood Presbyterian Hospital disclose that 120 patients had received treatment with arginase during 1951-52. The names of these patients were checked against the death records of the State Department of Public Health in May 1953. In 70 cases, cancer was listed as the cause of death. This does not include all the cases dead of cancer, since some had out of state residences and returned thereto prior to decease.

8. *Autopsy Data Reviewed by Commission*

The autopsy data on the cases above referred to show, in the opinion of experienced pathologists, no evidence of specific effect of arginase on cancer. Microscopic sections available on the ten patients reviewed by the Hollywood Presbyterian Hospital Committee have been studied by Drs. Fred Stewart and Frank Foote of the Memorial Center in New York, by a pathologist on the staff of the University of Rochester Medical School, and by Dr. Harry Goldblatt, director, Institute for Medical Research, Cedars of Lebanon Hospital. None of them was able to report any specific or unusual microscopic findings indicative of specific change in the neoplasms from the treatment given.

9. *Consultant and Other Reports*

The Cutter Laboratories of Berkeley assigned a full-time research worker to observe the arginase work at the Hollywood Hospital in February 1952. On April 3, 1952, Mr. F. A. Cutter wrote to the Cancer Commission, ". . . we found insufficient objective evidence of therapeutic value to cause us to divert our current research from other channels. We therefore terminated what has amounted to an option on a license agreement."

In the 1952 annual report of Cutter Laboratories to stockholders this was referred to as follows:

"Some of the company's stockholders have asked what made Cutter's stock go up so fast early in the year and what made it fall the same way later in the year.

"An unfortunate rumor got started that we were on the verge of coming out with a cancer cure. Like most rumors, there was a grain—but only a grain—of truth in it.

"We were investigating a so-called cancer cure which turned out disappointingly, as have dozens of other similar products we have investigated in the past. When this became known, quite a few sold stock and toward the end of the year, when the stock was down, there was further selling, presumably to establish capital losses."

The Cancer Committee of the Hollywood Presbyterian Hospital after reviewing the cases treated by Dr. Boyd, recommended in March 1952 that no further patients be treated with arginase; this was approved by the medical advisory board of the hospital and accepted by its administration. The latter decided that, until the original animal experiments could be confirmed by competent authorities, no further patients were to be treated.

The cases presented and the case histories discussed by Dr. Boyd at the February 1952 meeting of the Hollywood Presbyterian Hospital Cancer Committee were reported to and reviewed by the Cancer Commission of the California Medical Association at its regular meeting in Los Angeles, April 26, 1952. Dr. Robert Scarborough, then chairman of the Commission, was authorized to state that: "*All available evidence to us indicates that arginase has no beneficial effects in the control of cancer in experimental animals or in patients. To date, it must be concluded that arginase is valueless.*" This statement was released to the press, and was published in California newspapers in April 1952.

10. *Conclusions of the Commission*

Arginase (also termed hepasyn) has been advocated for the treatment of cancer. The current proponents have claimed "near miraculous results."

The Cancer Commision has collected information on more than 26 patients treated with arginase, at least six of whom are now dead with the disease. Of those alive, no patient has been found with objective evidence of control of cancer under treatment with arginase or hepasyn alone.

The hospital in which the treatments were given in 1951 and 1952 lists 120 patients as having received arginase; by May of 1953, 70 of these patients were known to be dead with cancer.

Autopsy studies disclosed no evidence of specific chemotherapeutic effect.

There is no evidence to date that arginase (or hepasyn) has a beneficial effect on patients with cancer.

REFERENCES

1. Vrat, Ved: Symposium on arginase in cancer research, Permanente Foundation Med. Bull., 9:49-70, 1951.

2. Irons, W. G., and Boyd, E. F.: Arginase as an anticarcinogenic agent in mice and human beings, Arizona Med., 9:39-44, 1952.

Council Meeting Minutes

Tentative Draft: Minutes of the 401st Meeting of the Council, San Francisco, July 25, 1953.

The meeting was called to order by Chairman Shipman in the Golden Empire Room of the Hotel Mark Hopkins, San Francisco, at 9:30 a.m., Saturday, July 25, 1953.

Roll Call:

Present were President Green, President-Elect Morrison, Speaker Charnock, Secretary Daniels and Councilors West, Wheeler, Loos, Sampson, Pearman, Dau, Ray, Shipman, Lum, Bostick, Teall, Varden, Heron, Frees, Carey, Kirchner and Reynolds; absent for cause, Vice-Speaker Bailey and Editor Wilbur. A quorum present and acting.

Present by invitation during all or a part of the meeting were Messrs. Hunton, Thomas, Clancy, Gillette and Pettis of C.M.A. staff, legal counsel Hassard, Mr. Ben Read of the Public Health League of California, county society executive secretaries Watson of Sacramento, Wood of San Mateo, Donovan of Santa Clara, Jensen of Fresno, Geisert of Kern, Nute of San Diego and Bannister of Orange; Mr. K. L. Hamman of California Physicians' Service; and Drs. D. H. Murray, Wilton L. Halverson, John R. Upton, Francis J. Cox, Dan O. Kilroy, Christopher Leggo, John M. Kenney and James Doyle.

1. *Minutes for Approval:*

(a) On motion duly made and seconded, minutes of the 399th Council meeting, held May 23-27, 1953, were approved.

(b) On motion duly made and seconded, minutes of the 400th Council meeting, held May 28, 1953, were approved.

2. *Membership:*

(a) A report of membership as of July 18, 1953, was received and ordered filed.

(b) On motion duly made and seconded, one 1952 delinquent member and 57 members delinquent in 1953 were voted reinstatement.

(c) On motion duly made and seconded in each instance, eight applicants were voted Associate Membership. These were: Gordon Diddy, Fred C. Tongue, Glenn A. Young, Fresno County; Jeanne B. Blumhagen, Rex V. Blumhagen, Madera County; Merall Roth, Bernard M. Stone, San Francisco County; Helen M. Safford, San Joaquin County.

(d) On motion duly made and seconded in each instance, four applicants were voted Retired Membership. These were: Alfred M. Palmer, William Henry Sargent, Alameda-Contra Costa County; Philip Stephens, Los Angeles County; Lloyd D. Mottram, Stanislaus County.

(e) On motion duly made and seconded in each instance, a reduction of dues was granted to nine applicants who are suffering from protracted illness or undergoing postgraduate studies.

3. *Financial:*

(a) A report of bank balances as of July 18, 1953, was received and ordered filed.

(b) Mr. Hunton reported on his correspondence with New Mexico Physicians' Service and this was ordered filed.

4. *House of Delegates Actions:*

The Council reviewed two resolutions referred to it by action of the 1953 House of Delegates.

On Resolution No. 6, it was duly moved, seconded and voted to publish a map of California outlining the service areas of physicians in all parts of the state, to advise Dr. Burt Davis, author of the resolution, to this effect and inquire if such a map meets his request for a survey of medical service areas, to seek publicity on the Association's placement activities and to urge the Committee on Rural Health to continue its cooperation in the placement of physicians in areas of need.

On motion duly made and seconded, it was voted to request the C.M.A. Delegates to the A.M.A. to introduce resolutions in the A.M.A. looking toward a study of areas in need of additional medical service in all states.

On Resolution No. 7, introduced by Dr. Burt Davis, it was duly moved, seconded and voted to table.

5. *Medical Services Commission:*

Dr. Teall reported that the Medical Services Commission was considering its role in handling the recommendations of the C.P.S. Study Committee report, now referred to the commission. It was generally agreed that the commission was to serve as a source of information for the county societies, using all means at its command.

The matter of communication of news was also discussed and it was regularly moved, seconded and voted to expand the publication *Rx Reading* to include current items on health insurance and other factual material.

Dr. Teall also gave an illuminating report on his attendance at the meeting of the Cooperative Health Federation of America.

6. *Blood Bank Commission:*

Dr. Upton reported that four of the blood bank system banks had not secured a renewal of their contracts for production of blood for defense. He stated the commission was working with the Hemophilia Foundation of America for the supply of antihemophilia blood.

Dr. Upton suggested that legislation be secured to provide property tax exemption for premises used for non-profit blood banking purposes.

The blood banks in the system have produced 495,541 units of blood for defense and 54,647 units for civilian purposes since the current defense program started.

7. *Committee on Industrial Accident Commission:*

Dr. Francis J. Cox gave a progress report and expressed the hope that a more adequate schedule of industrial fees may be achieved in the very near future.

8. *Group Disability Insurance:*

Dr. Kirchner discussed the proposed program of disability insurance for Association members. Letters of approval or disapproval of the program from the insurance committees of several county societies were read and discussed.

On motion duly made and seconded, it was voted to approve the group disability insurance program proposed by the Lumbermans Mutual Insurance Co., through its broker, Charles O. Finley Co., for presentation to members of the California Medical Association.

9. *Committee on Industrial Health:*

Dr. Christopher Leggo, chairman of the Committee on Industrial Health, presented a revised statement of principles on nurses in industrial plants, previously approved by the Council and subjected to slight editing by the California State Nurses Association. Subject to Council approval, this statement could be issued jointly by the two associations. On motion duly made and seconded, the revised statement was approved.

Dr. Leggo also called attention to the fact that some physicians are declining from 25 to 43 per cent of job applicants where there is a history of back pain and the new employer may be held liable for its aggravation. He suggested this condition be watched over in coming months as a possible source of economic reaction due to the unemployability of the rejected applicants.

10. *Public Relations:*

Mr. Clancy reviewed the television program inaugurated July 12, 1953, as a public service program under the sponsorship of the Los Angeles County Medical Association and the California Medical Association. With minor changes this program could be made into a C.M.A. program suitable for telecasting in any area of the state.

A film reproduction of the initial telecast was shown.

11. *State Department of Public Health:*

Dr. Wilton L. Halverson, State Director of Public Health, reported an anticipated increase of polio-

myelitis cases in 1953 over the 1952 total of about 4,000. However, the incidence of paralysis is running about 46 per cent this year, compared with about 64 per cent in 1952. He discussed the use of gamma globulin for both mass inoculations and treatment of family contacts of clinically diagnosed polio cases, stating the greater chance of immunization lay in the family contact groups.

On motion duly made and seconded, the Committee on Public Health and Public Agencies was authorized to cooperate with Department of Public Health in the event of mass inoculations and to seek further cooperation from the county societies.

Dr. Halverson reported the incidence of encephalitis appeared low this year.

12. *Health Education:*

Dr. John M. Kenney, Santa Rosa, discussed the need of cooperating with the schools and other agencies in fostering adequate and accurate education on health subjects. The subject was taken under advisement.

13. *Legal Department:*

Mr. Hassard gave a progress report on the San Diego lawsuit, on which final briefs have been filed and oral arguments made before the appeals court.

14. *California Physicians' Service:*

Dr. Heron reported 605,274 beneficiary members and 11,157 physician members of California Physicians' Service as of June 30, 1953. The beneficiary membership showed a gain of 29,330 for the second calendar quarter. He also reported progress in the joint meetings between C.P.S. and Blue Cross representatives and stated that one basic contract has been developed to replace seven types of contracts previously used. Additional benefits may be added to the basic contract in specific instances. Mr. K. L. Hamman presented a financial report.

15. *Public Policy and Legislation:*

Dr. Dwight H. Murray and Mr. Ben H. Read gave a report on legislation adopted by the state's 1953 legislature and now pending before Congress. It was pointed out that all measures sponsored by the C.M.A. in the 1953 state legislative session had been adopted and signed into law.

16. *Advisory Planning Committee:*

Mr. Hunton reported the Advisory Planning Committee had met July 24, had approved the kinescoping of the Los Angeles television program for use in other areas and had approved the issuance of a new "Welcome" pamphlet to be sent to new members of the Association.

Proposed Constitutional Amendment

(First Publication)

Following is the proposed amendment to the Constitution of the California Medical Association that was introduced at the 1953 Annual Session and was carried over for action at the Interim Session. It has been referred to Reference Committee No. 4, which is to make its report upon it available to delegates at least 30 days before the opening of the 1953 Interim Session in San Francisco, December 12, 1953. California Medical Association members who wish to record opinions on the proposed amendment may send them to the chairman of Reference Committee No. 4, Albert G. Miller, M.D., 77 San Mateo Drive, San Mateo.

Submitted by Sidney J. Shipman, for the Council, May 24, 1953.

Resolved: That Article III, Part A, Section 1 of the Constitution of this Association, the California Medical Association, be amended by striking out the word "District" in subsection (c) of said Section 1, so that Section 1 will read as follows:

Section 1—Composition

"The House of Delegates shall consist of:

"(a) Delegates elected by the members of the component societies;

"(b) Officers of the Association as hereinafter provided;

"(c) Ex-officio, with the right to vote, the Councilors, and

"(d) Ex-officio, without the right to vote, the Past Presidents."

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17. *Committee on the Unlawful Practice of Medicine:*

Dr. Shipman made a progress report on the activities of the Committee on the Unlawful Practice of Medicine.

18. *San Diego Television Program:*

On motion duly made and seconded, it was voted to provide consultation service to the San Diego County Medical Society in the production of a television program to originate there.

19. *Orange County Medical Association:*

On motion duly made and seconded, it was voted to extend to the Orange County Medical Association the sincere thanks of the Association for having performed an outstanding job in rechecking the physical status of 50,000 Boy Scouts prior to their admission to the Jamboree held in Orange County. It was pointed out that 201 Orange County members had signed up to do the rechecking and all but one or two appeared as scheduled.

20. *Use of C.M.A. Mailing List:*

On motion duly made and seconded, it was voted to approve the use of the Association's mailing list by the San Francisco Heart Association in publicizing a scientific meeting.

21. *World Medical Association:*

On motion duly made and seconded, it was voted to appropriate $1,000 toward the activities of the World Medical Association. A three-fourths vote noted.

22. *Committee on Rural Health:*

On motion duly made and seconded, it was voted to approve the plan of Dr. Henry Randel, chairman of the Committee on Rural Health, to seek the names of additional committee members for appointment by the Council.

23. *Vocational Nursing:*

Dr. Morrison reported on a meeting with an organization of vocational nurses and it was agreed he should maintain this contact.

Adjournment:

There being no further business to come before it, the meeting was adjourned at 6:25 p.m.

SIDNEY J. SHIPMAN, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

Nursing Services in Industry

A statement of principle made jointly by the California Medical Association and the California State Nurses Association

THE CALIFORNIA MEDICAL ASSOCIATION and the California State Nurses Association have reviewed the contribution to industrial health made by the members of the nursing profession through the individual activities of the nurses employed by and in industry. Through their contact with individual employees and with members of management, nurses have furthered public health education, the use of community resources, improved personal and plant hygiene, healthier psychological relationships between management and workers, and a closer liaison between the plant employee and the practicing physician.

It is also recognized, however, that demands are made by both employees and management upon nurses in industry to engage in activities which appear to encroach upon the practice of medicine as defined by the California Medical Practice Act. If the nurse accedes to these demands, she is jeopardizing her professional status and her very livelihood.

It is urged that the nurse in industry, having met a particular emergency with which she is confronted, protect herself, her patient and her employer by referring the patient to a physician for diagnosis or medical care when either is required, and that further treatment be carried on only under such medical supervision. Employers of nurses are urged to facilitate and encourage such referrals, in order that they themselves may be protected against being involved in violations of the Medical Practice Act.

Technicalities of the Medical Practice Act are difficult to translate into lay language and no simple definition can be given as to what services may be rendered with impunity. It certainly may be said, however, that any injury serious enough to cause even temporary disability or which requires more than protective dressing, or which does not respond favorably to procedures which are commonly considered to be emergency nursing procedures requires medical treatment.

It must be borne in mind that, regardless of the wishes of the patient or his personal needs, or the demands of the employer in regard to industrial injuries, a nurse is forbidden by law to either diagnose or treat medical conditions or surgical injuries. Only as this fact is fully understood by employees and employers alike will the pressure upon the nurse to exceed her functions be lessened.

It is essential that every nurse and her industrial employer be thoroughly conversant with the Medical Practice Act and its implications. It must be remembered that the law cannot be ignored. A violation remains a violation whether committed ignorantly or knowingly.

The California Medical Association and the California State Nurses Association anticipate and welcome the further extension of employment of nurses in industry in view of their contributions both to the overall health and to the physical and emotional welfare of employed individuals. Both organizations look forward to establishing and maintaining the area in which the professional industrial nurse may function effectively, efficiently, ethically and legally.

CALIFORNIA MEDICAL ASSOCIATION

Annual Meeting

LOS ANGELES
May 9-13, 1954

Papers for Presentation

If you have a paper that you would like to have considered for presentation, **it should be submitted to the appropriate section secretary** (see list on this page) not later than November 15, 1953.

Scientific Exhibits

The space available for scientific exhibits is limited. If you would like to apply for space, please write immediately to the office of the California Medical Association, 450 Sutter Street, San Francisco 8, for application forms. To be given consideration by the Committee on Scientific Work, the forms, completely filled out, must be in the office of the California Medical Association not later than December 1, 1953. (No exhibit shown in 1953, and no individual who had an exhibit at the 1953 session, will be eligible until 1955.)

SCIENTIFIC PAPERS . . .

. . . SCIENTIFIC EXHIBITS

PLANNING MAKES PERFECT

AN EARLY START HELPS

SECRETARIES OF SCIENTIFIC SECTIONS

Allergy . . . . . *Lazarre J. Courtright*
490 Post Street, San Francisco 2

Anesthesiology . . . . . *Marshall L. Skaggs*
18 Hillcrest Road, Mill Valley

Dermatology and Syphilology . . *Walter F. Schwartz*
696 East Colorado Street, Pasadena 1

Eye, Ear, Nose and Throat—

Eye . . . . . *Alfred R. Robbins (Chairman)*
1930 Wilshire Boulevard, Los Angeles 57

ENT . . . . . *Francis A. Sooy*
490 Post Street, San Francisco 2

General Medicine . . . . . *Edgar Wayburn*
490 Post Street, San Francisco 2

General Practice . . . . . *Joseph W. Telford*
3255 Fourth Avenue, San Diego 3

General Surgery . . . . . *William Brock*
2633 Pacific Avenue, Stockton 4

Industrial Medicine and Surgery . . . . *Verne G. Ghormley (Asst. Secty.)*
2014 Tulare Street, Fresno

Obstetrics and Gynecology . . . *Charles T. Hayden*
411 Thirtieth Street, Oakland 9

Pathology and Bacteriology . . . . . *Paul Michael*
450 Thirtieth Street, Oakland 9

Pediatrics . . . . . *Gordon F. Williams*
1111 University Drive, Menlo Park

Psychiatry and Neurology . . . *George N. Thompson*
2010 Wilshire Boulevard, Los Angeles 57

Public Health . . . . . *L. S. Goerke*
116 Temple Street, Los Angeles 12

Radiology . . . . . *H. R. Morris*
1027 "D" Street, San Bernardino

Urology . . . . . *Thomas I. Buckley*
431 Thirtieth Street, Oakland 9

In Memoriam

ABRONS, HARRY. Died in New York City, June 4, 1953, aged 70, of angina pectoris. Graduate of Columbia University College of Physicians and Surgeons, New York, 1909. Licensed in California in 1910. Doctor Abrons was a retired member of the Alameda-Contra Costa County Medical Association, the California Medical Association, and an associate member of the American Medical Association.

✤

AVERY, JOHN W. Died recently, aged 85. Graduate of the University of Vermont College of Medicine, Burlington, 1897. Licensed in California in 1923. Doctor Avery was a retired member of the Los Angeles County Medical Association, the California Medical Association, and an associate member of the American Medical Association.

✤

BLACK, EMIL C. Died in San Diego, July 2, 1953, aged 78. Graduate of the University of Nebraska College of Medicine, Omaha, 1903. Licensed in California in 1914. Doctor Black was a retired member of the San Diego County Medical Society, the California Medical Association, and an associate member of the American Medical Association.

✤

BURKE, DONALD W. Died in Salinas, July 8, 1953, aged 57. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1924. Licensed in California in 1924. Doctor Burke was a member of the Alameda-Contra Costa Medical Association, the California Medical Association, and the American Medical Association.

✤

BROOKS, LEROY. Died in the Bohemian Grove encampment on the Russian River, August 1, 1953, aged 60, of coronary artery disease. Graduate of Marquette University School of Medicine, Milwaukee, Wis., 1920. Licensed in California in 1921. Doctor Brooks was a member of the San Francisco Medical Society, the California Medical Association, and the American Medical Association.

✤

EIKENBERRY, KENNETH W. Died in Hollywood, July 15, 1953, aged 47. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1937. Doctor Eikenberry was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

HAIG, THOMAS R. Died in San Francisco, July 13, 1953, aged 57, of coronary artery disease. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1922. Licensed in California in 1922. Doctor Haig was a member of the Sacramento Society for Medical Improvement, the California Medical Association, and the American Medical Association.

✤

HERSHBERGER, LLOYD R. Died in Los Angeles, June 14, 1953, aged 47. Graduate of Northwestern University Medical School, Chicago, Ill., 1931. Licensed in California in 1931. Doctor Hershberger was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

INGALLS, ALBERT T. Died May 1, 1953, aged 79. Graduate of the Indiana Medical College School of Medicine of Purdue University, Indianapolis, 1906. Licensed in California in 1919. Doctor Ingalls was a member of the Los Angeles County Medical Association, the California Medical Association, and an associate member of the American Medical Association.

✤

SARGENT, WILLIAM H. Died in Oakland, July 29, 1953, aged 71, of coronary thrombosis. Graduate of Bennett Medical College, Chicago, Ill., 1905. Licensed in California in 1920. Doctor Sargent was a member of the Alameda-Contra Costa Medical Association, the California Medical Association, and an associate member of the American Medical Association.

✤

STEWART, JOHN N. Died in Santa Maria, July 18, 1953, aged 44, of adenocarcinoma of the pancreas. Graduate of the University of Nebraska College of Medicine, Omaha, 1932. Licensed in California in 1940. Doctor Stewart was a member of the Santa Barbara County Medical Society, the California Medical Association, and the American Medical Association.

✤

WHALEN, JOHN A. Died in Los Angeles, March 27, 1953, aged 60, of bronchogenic carcinoma. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1925. Doctor Whalen was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Doctors of medicine, discussing health topics of general interest to the public, have been appearing on television in the Los Angeles area each week since July 12, 1953, under the auspices of the California Medical Association and the Los Angeles County Medical Association. The program, titled **"Ask the Doctor,"** is presented as a public service feature by Station KTLA for a half hour beginning at noon every Sunday. Production, under the supervision of the CMA, is being managed by Bill Tobitt, former Orange County Medical Association executive secretary. Program content and participating doctors are determined by the radio and television committee of the LACMA.

Subjects presented during the first seven weeks dealt with sunburn, obesity, children's accident prevention, rheumatic fever and mitral stenosis, crossed eyes, poliomyelitis and tuberculosis. The number of physicians has varied from two to four for each program, with Gil Martyn, station feature events chief, serving as coordinator of their discussions.

The title has a direct implication in that viewers are invited to telephone their questions while a program is in progress, in addition to writing in questions on a topic announced for the succeeding week. There has been an excellent and complimentary response of mail thus far.

* * *

Guest speakers at the Annual Symposium of Cardiac Disease to be presented by the **Los Angeles County Heart Association** at the Wilshire Ebell Theatre, Los Angeles, October 20-21, will be: George Burch, M.D., New Orleans, Tulane University School of Medicine; Lewis Dexter, M.D., Boston, Harvard Medical School; Harald Eliasch, M.D., Stockholm, St. Erik's Hospital; and Paul Wood, M.D., London, Institute of Cardiology. (Detailed program on page 262.)

SAN DIEGO

The California Academy of General Practice will hold its Fifth Annual Scientific Assembly at the Hotel del Coronado, Coronado, October 25, 26 and 27.

Twenty scientific papers will be presented on a variety of medical, obstetrical and surgical subjects. Among the many noted speakers are Louis Buie, M.D., senior consultant Department of Proctology, Mayo Clinic; Alfred C. Kinsey, Ph.D., professor of zoology, Indiana University; Raymond McNealy, M.D., professor of surgery, Cook County Postgraduate School of Medicine, Chicago; and F. H. Bentley, M.D., formerly professor of surgery, University of Durham, England, and now lecturer in surgery, Sommer Memorial Trust, Portland, Oregon.

More than 1000 physicians from California, Oregon, Nevada and Arizona are expected to attend. The meeting is open to all members of the Academy and to any non-member doctor of medicine upon payment of a $5 registration fee. Further information may be had from the California Academy of General Practice, Suite 900, 461 Market Street, San Francisco 5.

SAN FRANCISCO

The 20th Annual Meeting of the **American College of Chest Physicians** will be held in San Francisco, June 17-20, 1954. Californians currently holding office in the organization are Dr. Seymour M. Farber, San Francisco, who was reelected regent-at-large of the College at the annual meeting in May; Dr. Buford H. Wardrip, San Jose, governor of the College for California; and Dr. E. W. Hayes, Monrovia, who was reelected chairman of the Council on Undergraduate Medical Education.

* * *

The San Francisco Heart Association will hold its 24th annual postgraduate **symposium on heart disease** October 28-30, 1953, at the St. Francis Hotel, San Francisco, in cooperation with the Heart Associations of Alameda, Contra Costa, Monterey, San Mateo and Santa Clara counties.

Guest speakers will be Robert H. Bayley, M.D., Oklahoma City; Herrman Blumgart, M.D., Boston; Howard B. Burchell, M.D., Rochester, Minn.; Robert L. King, M.D., Seattle; Ann G. Kuttner, M.D., New York City; Howard B. Sprague, M.D., Boston; Eugene A. Stead, Jr., M.D., Durham, N. C.; Lewis Thomas, M.D., Minneapolis; Francis C. Wood, Philadelphia, and Paul Wood, M.D., London. (Detailed program on page 262.)

GENERAL

Books for Israel is making a plea to physicians who have medical books (published since 1940) that they no longer use, to send them parcel post prepaid, to Books for Israel, 115 King Street, New York 1, N. Y., for transshipment to Israel where they are badly needed.

It was pointed out that up to 70 pounds may be sent by parcel post at eight cents for the first pound and four cents for each additional pound, marked "BOOK RATE." Request was made that the return address of the individual or organization sending books be given so that the gift may be acknowledged. Funds for shipment from New York to Israel have been provided under Point IV, U. S. State Department, sponsors of this project, it was said.

* * *

Information on the latest developments aimed at preventing disease and promoting personal and public health will be exchanged by professional workers from all parts of the free world at the 81st annual meeting of the **American Public Health Association** and annual sessions of 40 related organizations at the Hotels Statler and New Yorker, New York City, November 9-13.

More than 5,000 public health workers—physicians, dentists, nurses, engineers, statisticians, veterinarians, sanitarians, nutritionists, health educators, entomologists, biologists and others—are expected to attend the sessions, according to the association's executive secretary, Dr. Reginald M. Atwater.

* * *

The American Goiter Association has announced the opening of the annual contest for the **Van Meter Prize Award** of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the association which will be held in Boston, Massachusetts, April 29, 30 and May 1, 1954, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English, and a typewritten double-spaced copy in duplicate sent to the corre-

sponding secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York, not later than January 15, 1954.

* * *

Ten special **grants** totalling $71,070 to aid research projects in California were announced recently by the California Division of the **American Cancer Society.** They were:

$25,255 to the University of California at Berkeley, $16,451 of that amount to be used for tumor host studies and $8,804 to be used in support of a follow-up study of cancer patients in the departments of the University School of Medicine.

$21,150 to the Los Angeles County General Hospital for continuation of cancer research projects already under way, and for completion of an analysis of the hospital's chest tumor registry which may help determine whether or not the mass x-ray survey technique is effective in detection of cancer of the lung.

$10,000 to Stanford University. Of that amount, $5,000 is for continuation of studies on the role of the pituitary and adrenals in cancer development and $5,000 for studies on the characterization and function of important biochemical fractions.

$7,065 to the University of San Francisco in support of research on the structure of chromosomes by Dr. William Hovanitz, professor of biology.

$5,000 for tissue culture studies of carcinoma of the uterine cervix at the University of California at Los Angeles.

$2,000 to the Rees-Stealy Clinic Research Foundation in San Diego for study of the *in vivo* metabolism of radioactive estrogens.

$600 to the University of Southern California for emergency support of a study of the capacitance of bladder mucosa.

POSTGRADUATE EDUCATION NOTICES

LOS ANGELES HEART ASSOCIATION

October 20-21, Wilshire Ebell Theatre, Los Angeles

Symposium on Cardiac Disease

TUESDAY, OCTOBER 20, 1953

MORNING

9:30—Opening remarks by Edgar F. Mauer, M.D., President of the Los Angeles County Heart Association.

9:45—Four Year Follow-up of Rheumatic Fever Patients Treated with ACTH and Cortisone, George Griffith, M.D.

10:05—Unappreciated Physical Signs Important in Cardiovascular Diagnosis—Paul Wood, M.D.

10:35—Use of the Dye Dilution Technique for Determination of Cardiac Output in Pre- and Postoperative Valvular Heart Disease—Albert A. Kattus, M.D., Gilbert F. Sofio, M.D., Aaron A. Cohen, M.D., and Arthur U. Rivin, M.D.

10:55—Some Aspects of the Mechanism of Congestive Heart Failure—George Burch, M.D.

11:25—Curable Heart Disease—Lewis Dexter, M.D.

AFTERNOON

Symposium on the Surgical Relief of Mitral Stenosis

1:30—Mitral Insufficiency: Its Diagnosis and Its Effect on Valvulotomy for Mitral Stenosis—Lewis Dexter, M.D.

2:00—The Effects of Mitral Valvular Disease on Renal Hydrodynamics—Harald Eliasch, M.D.

3:30—Roundtable Presentation and Discussion: Valvulotomy for Mitral Stenosis—Selection of patients, role of cardiac catheterization, pre- and postoperative care and results—George Burch, M.D., Lewis Dexter, M.D., Harald Eliasch, M.D., George Griffith, M.D. Paul Wood, M.D., and William Paul Thompson, M.D., moderator.

WEDNESDAY, OCTOBER 21

MORNING

9:30—The Recognition of Giant Dilatation of the Left Auricle—R. C. Pollock, M.D.

9:45—The Comparison of Humoral and Neurogenic Factors in Human Hypertension by Bioassay with Hexamethonium—Daniel Green, M.D.

10:05—Experiences in the Surgical Relief of Aortic Stenosis—William H. Muller, Jr., M.D., Albert A. Kattus, Jr., M.D., and J. Francis Dammann, Jr., M.D.

10:55—Intramural Depolarization Potentials in Myocardial Infarction—Myron Prinzmetal, M.D., Rexford Kennamer, M.D., Clinton Shaw, M.D., Noboru Kimura, M.D., Inga Lindgren, M.D., Morton Maxwell, M.D., Jacob L. Bernstein, M.D., and Alfred Goldman, M.D.

AFTERNOON

1:30—Cor Pulmonale and Hypoxia—Lewis Dexter, M.D.

2:30—The Continental Viewpoint on Pulmonary Hypertension—Paul Wood, M.D.

3:00—Three-Year Study of Atherosclerosis and Arteriosclerosis by the Chylomicron Index—George Griffith, M.D.

3:15—The Protective Value of Pulmonary Valvular Stenosis in Certain Forms of Congenital Heart Disease—Louis E. Martin, M.D., Sidney S. Sobin, M.D., Harvey A. Humphrey, M.D., John L. Johnson, M.D., and Eugene Temkin, M.D.

3:30—Experimental Production of Congenital Cardiac Lesions in the Rat—Sidney S. Sobin, M.D., Marjory H. Fox, and Betty Davis.

3:50—The Low Salt Syndrome: Its Recognition and Treatment—George Burch, M.D.

SAN FRANCISCO HEART ASSOCIATION

October 28-30, St. Francis Hotel, San Francisco

24th Annual Symposium on Heart Disease

WEDNESDAY, OCTOBER 28

MORNING

9-12—Session on Electrocardiography and Other Graphic Diagnostic Methods—David A. Rytand, M.D., presiding.

9-10:30—Electrocardiographic Pathological Conference—Moderator: David A. Rytand, M.D.; participants: Robert H. Bayley, M.D., Howard B. Burchell, M.D., Howard B. Sprague, M.D., Francis C. Wood, M.D., and Paul Wood, M.D.

10:45-11:20—Considerations of the Foundation of Vectorcardiography—Robert H. Bayley, M.D.

11:20-11:55—The Clinical Value of Phonocardiography—Howard B. Sprague, M.D.

AFTERNOON

Presiding: Edward Campion, M.D., President, Northern California Pediatric Society

1:30-2:30—Therapy of Rheumatic Diseases—A panel discussion. Moderator: Lowell A. Rantz, M.D.; participants: Ann G. Kuttner, M.D., Lewis Thomas, M.D., and Paul Wood, M.D.

2:30-3:00—Appreciation of Physical Signs—Paul Wood, M.D.

3:15-4:00—New Techniques in the Diagnosis of Congenital Heart Disease with Particular Regard to Dye Dilution Curves—Howard B. Burchell, M.D.

4:00-5:00—Cardiac Involvement in Non-Cardiac Pediatric Conditions—A panel discussion. Moderator: Henry Brainerd, M.D.; participants: Howard B. Burchell, M.D., Mary B. Olney, M.D., Ann G. Kuttner, M.D., and Lewis Thomas, M.D.

THURSDAY, OCTOBER 29

MORNING

Presiding: Alfred Goggio, M.D.
Past President, Alameda County Heart Association

9:00-10:00—Present Status of Modern Cardiac Surgery—a panel discussion. Moderator: Alfred Goggio, M.D.; participants: Howard B. Burchell, M.D., Frank Gerbode, M.D., H. Brodie Stephens, M.D., and Paul Wood, M.D.

10:00-10:45—Unusual Forms of Heart Disease—Howard B. Burchell, M.D.

11:00-12:00—Mitral Valve Disease—Paul Wood, M.D.

AFTERNOON

Presiding: Robert L. Smith, Jr., M.D.

1:30-2:30—The Pathology and Clinical Classification of Cardiac Pain—Herrman Blumgart, M.D.

2:30-3:30—Controversial Issues in the Management of Myocardial Infarction—Howard B. Burchell, M.D.

3:45-5:00—Panel Discussion on Chronic Coronary Disease. Moderator: Robert L. Smith, Jr., M.D.; participants: Herrman Blumgart, M.D., Robert L. King, M.D., Eugene A. Stead, Jr., M.D., and Howard B. Sprague, M.D.

FRIDAY, OCTOBER 30

MORNING

Presiding: Maurice Eliaser, Jr., M.D., President, San Francisco Heart Association

9:00-9:15—President's Address: Maurice Eliaser, Jr., M.D.

9:15-9:30—Greetings from the President of the American Heart Association—Robert L. King, M.D.

9:30-10:30—The Treatment of Cardiac Emergencies—Herrman Blumgart, M.D.

10:45-11:15—Present Views in Circulatory Failure—Eugene A. Stead, Jr., M.D.

11:15-12:15—Cardiac Drugs—a panel discussion. Moderator: Maurice Eliaser, Jr., M.D.; participants: Herrman Blumgart, M.D., Robert L. King, M.D., Howard B. Sprague, M.D., Eugene A. Stead, Jr., M.D., and Paul Wood, M.D.

AFTERNOON

1:30-5:00—Clinical Session, Nurses' Auditorium, Mount Zion Hospital. Presiding: Arthur L. Bloomfield, M.D.; participants: Herrman Blumgart, M.D., Howard B. Burchell, M.D., Robert L. King, M.D., Howard B. Sprague, M.D., Eugene A. Stead, Jr., M.D., Francis C. Wood, M.D., and Paul Wood, M.D.
It is planned to illustrate the following subjects: Hypertension, Bacterial Endocarditis, Mitral Valve Disease, Myocarditis, Pulmonary Hypertension, and others.

UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE

Cardiology and Vascular Disease—No. 832

Date: September 14, 1953—full time, one year.

Fee: $1,000.00.

History, physiology, pathology, diagnosis, treatment of cardiac and peripheral disease. Emphasis placed on bedside teaching, electrocardiography, fluoroscopy, and associated diagnosis aids. Designed to meet the requirements for certification by the American Board of Cardiology. Six hours of didactic lectures per week; 35 hours of laboratory work. 32 units credit for master's degree. Course Director: George C. Griffith, M.D.

Gastroenterology—No. 844

Date: September 21, 1953—Full time, one year.

Fee: $1,000.00.

Course is designed to give a limited number of qualified physicians advanced training in this field. The didactic courses will include intensive study of the physiology, pathology, as well as the clinical aspects of the diseases of the digestive tract. Clinical teaching will be done in the outpatient department of the Los Angeles County Hospital. 32 units credit for master's degree. Course Director: George K. Wharton, M.D.

Diagnostic and Therapeutic Radiology—No. 858

Date: Course begins by arrangement.

Fee: 3 mos.—$250.00 6 mos.—$ 500.00
9 mos.—$750.00 12 mos.—$1,000.00

This course is designed for a limited number of qualified physicians who wish to prepare for the American Board of Radiology, and who wish specialized training in a particular field of medicine such as orthopedics, cardiology, etc. Course will be conducted in the Department of Radiology at the Los Angeles County Hospital. Course Directors: Ray A. Carter, M.D., George Jacobson, M.D.

Anesthesia

Date: Course begins by arrangement.

Fee: $300.00 (full time, three months).

Basic principles and techniques involved in administering the various anesthetic agents, including oxygen therapy and operating room care of patients. Open to a limited number of qualified physicians and dentists. Emphasis placed on practical administration of anesthetic agents. Presented at the Los Angeles County Hospital. Course Director: J. S. Denson, M.D.

Contact: Gordon E. Goodhart, M.D., University of Southern California School of Medicine, Division of Medical Extension Education, 1200 North State Street, Box 158, Los Angeles 33, California.

COLLEGE OF MEDICAL EVANGELISTS

Full-Time Basic Science Course in Surgery and Surgical Specialties

Date: October 5, 1953 through June 11, 1954.

Fee to be announced.

Contact: H. M. Walton, M.D., Chairman, Postgraduate Division, 312 North Boyle Avenue, Los Angeles 33.

RESEARCH STUDY CLUB OF LOS ANGELES

23rd Annual Clinical Convention of Ophthalmology and Otolaryngology

Date: January 18 through January 29, 1954. Each applicant must be a member in good standing of the American Medical Association in order to become eligible for attendance.

Fee: $100.00.

Contact: Pierre Violé, M.D., Treasurer, 1930 Wilshire Boulevard, Los Angeles 5, Calif.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES

In Long Beach (in cooperation with the Long Beach Branch, Los Angeles County Medical Association)

Clinical Medical Seminars

Date: September 23, 1953-June 23, 1954, One Wednesday per month, 2-5 p.m.

Fee: $50.00.

In Los Angeles:

1. Annual Postgraduate Medical Seminars.

Date: September 21-December 7, weekly panel presentations.

Fee: $50.00.

2. Dermatology in General Practice (limited to 20 students).

Date: October 7-November 11.

Fee: $30.00.

3. Surgical Anatomy (limited to 30 students).

Date: November 5, 1953-January 27, 1954.

Fee: $75.00.

4. Photography in Medical Practice and Research.

Date: September 30-December 16.

Fee: $50.00.

5. Dermatology Conference.

Date: February 11, 12, 1954.

Fee: $35.00.

6. Anesthesiology.

Date: Spring, 1954.

Fee: Details to be announced.

7. Fundamental Principles of Radioactivity, including Clinical Use of Radioisotopes.

Date: September-June.

Fee: $700.00.

40 weeks—200 hours (including 80 hours clinical).

Contact: Mrs. Margaret H. Griffith, Assistant Head, Postgraduate Instruction, Medical Extension, University of California, Los Angeles 24, California.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Evening Lectures in Medicine, Mills Memorial Hospital, San Mateo.

Date: September 17-December 10.

Medicine for General Practitioners, East Oakland Hospital.

Date: September 22-December 8.

Ophthalmology, University Extension Building, 540 Powell Street, San Francisco.

Date: December 2, 3, 4, 5 (changed from September 7-12).

Contact: Office of Medical Extension, University of California School of Medicine, University of California Medical Center, San Francisco 22, California.

STOCKTON POSTGRADUATE STUDY CLUB

Fall Lecture Series, 1953

Sept. 17—Management of Coronary Artery Disease—George Griffith, M.D., University of Southern California, Los Angeles.

Sept. 24—Acute Intestinal Obstruction—Orville Grimes, M.D., University of California Hospital, San Francisco.

October 8—Problem of the Nervous Patient—Alfred Overbach, M.D., San Francisco.

October 15—Recent Advances in the Practical Use of Hormones—Peter Forsham, M.D., University of California Hospital, San Francisco.

October 22—Diagnostic and Therapeutic Errors in the Handling of Tumors from the Standpoint of a Pathologist—Warren Bostick, M.D., University of California Hospital, San Francisco.

October 28—Differential Diagnosis of Urological Signs and Symptoms—Donald Smith, M.D., University of California Hospital, San Francisco.

November 12—Diagnosis and Treatment of Common Skin Diseases—Eugene M. Farber, M.D., Stanford Hospital, San Francisco.

November 19—Treatment of Infertility, Sterility and Habitual Abortion—Abraham R. Abarbanel, M.D., College of Medical Evangelists, Los Angeles.

SEMINARS OF THE ALUMNI COMMITTEE OF THE CHILDREN'S HOSPITAL, SAN FRANCISCO

Oct. 31, 1953—Naevi, Tumors and Malignancies in Childhood—10:00-4:30.

December 5, 1953—Surgery and Anesthesia in Childhood, with a discussion on the effects of hospitalization on the young child for surgical procedures.

January 23, 1954—The Problems of Prematurity and the Newborn Infant.

March 30, 1954—Acute and Chronic Infections and the Choice of Antibiotics in Treatment.

April 24, 1954—Childhood Ecology, with a discussion of physical, mental and emotional growth and development of the young child; the effects of deprivation of maternal care, and the impact of environment on the child.

A fee of $15.00 will be charged for attendance at all the seminars and those who wish to have further details or be on the mailing list for such details may write to: H. E. Thelander, M.D., Children's Hospital, 3700 California Street, San Francisco.

INFORMATION

Union Labor Health and Welfare Insurance Plans

The Present Status in the San Francisco Bay Area

SAMUEL R. SHERMAN, M.D., San Francisco

THE HEALTH of trade union members has been a subject for union interest ever since 1893. It is true that extensive health insurance programs now being advocated are of comparatively recent development but only as far as they are considered issues related to collective bargaining. Provision for the financial protection of members against wage losses due to illness was among the earliest beneficial activities of trade unions. Barbers, who were organized in 1887, offered sick benefits to their membership in 1893. Tobacco workers and pattern makers provided such benefits as early as 1896. However, the whole history of union sickness benefits has been a troubled one. Many of the plans were begun on an inadequate financial basis. The following is a quotation from a bulletin recently released by the American Federation of Labor regarding the early health benefit plans: "Unions have sponsored their own benefit plans for decades. Often actuarially unsound, and over-ambitious in scope, many of these plans collapsed." In 1933 twenty unions reported payments of sickness benefits. In 1943 there were still only eighteen such reports.

What, then, brought about the renewed interest in health and welfare programs, and when did they start their swing into the labor limelight?

The inclusion of health and welfare programs in labor contracts is a wartime development. During the period of the wage stabilization program efforts were made to secure "fringe benefits" in lieu of proposed wage increases. The War Labor Board acted kindly toward proposals for sickness pay and approved complete health protection programs, if the employer was agreeable. More often than not he was. This stimulated growth of the plans.

There are many problems which must still be faced in the development of union health and welfare programs. There are many kinds of program in effect and many new kinds which are being advocated. A single ideal program cannot be evolved to meet equally the needs of different employee groups. Insurance advisors have warned the unions that the plans must have a sound actuarial basis or they will soon disintegrate because of their own inherent weaknesses. Occupation, age and sex of the group must be considered in developing the plan, and problems of administration should be carefully considered.

As far as the relation of the plans to public health insurance is concerned, it is felt that the unions have, at least temporarily, given up the idea of the government providing them with sickness insurance. Walter Reuther, president of the CIO, has said: "There is no evidence to encourage the belief that we may look to Congress for relief. In the immediate future, security will be won for our people only to the extent that the union succeeds in obtaining such security through collective bargaining." The aims of practical "here and now" unionism are being put into effect without waiting for the government to launch any cumbersome compulsory sickness insurance program.

Physicians are interested of course in the sociological and economic effects of the various union plans for medical care on the private practice of medicine.

An important item for consideration is the fact that 42 per cent of all medical care in the United States is now paid for by someone other than the patient: Government agencies, including county, state and federal, Veterans Administration and welfare agencies pay for 20 per cent of all services; 20 per cent more is paid for by employers; 2 per cent by philanthropic institutions. If the rate of growth continues it is logical to assume that as high as 70 per cent of medical services will be paid by someone other than the patient. Since management now has about 30 per cent of its payroll covering fringe benefits, management is beginning to take far more interest in what the employee gets for the money paid out, and will be far more concerned about medical care, since almost all union-negotiated contracts call for payment of all the cost by the employer.

The San Francisco Labor Council, consisting of 141 local American Federation of Labor unions that have approximately 187,000 workers with about 300,000 dependents, has approved for further consideration a city-wide health program which may greatly affect the union health and welfare patterns in many other cities of the United States. The Council early in 1952 hired a young physician, Dr. E. Richard Weinerman, to make a complete survey of all existing health and welfare plans in the San Francisco area, with special emphasis placed on those under A. F. of L. control. His survey, which took about three months, revealed the following: About half of the A. F. of L. members were already protected by existing health

Presented before the Section on Industrial Medicine and Surgery at the 82nd Annual Session of the California Medical Association, Los Angeles, May 24-28, 1953.

and welfare funds, and the number was expected to increase by 30 per cent by the end of 1952. These funds spent about $7,500,000 in 1951 for health coverage. The Labor Council officials claimed that this money could be spent more effectively through a proposed plan of health centers which were centrally administered, labor controlled, with closed panels of physicians. These centers would cost approximately $200,000 to $400,000 each to build and equip. According to Dr. Weinerman's findings, there was a confused and often overlapping pattern of union welfare funds in San Francisco, as in most other cities. Seventy-one local unions were involved, and 64 joint agreements, administered from 45 separate offices and covered under 24 different insurance carriers and health-service agreements. Eighty-six per cent of the coverage was through commercial insurance companies. The other coverage was supplied by California Physicians' Service, Permanente Health Plan, and Blue Cross. Only one-fifth of the covered workers had their dependents included in health benefits; about half had the option of covering their dependents by paying extra premiums.

It is claimed that in many plans the worker got back in actual "health value" only half the premium paid in his behalf. The rest assertedly was consumed by excessive administration expenses for filing, processing, and paying individual bills on each item of medical service.

Dr. Weinerman's proposal of union-dominated health centers with closed panel staffs would in theory provide comprehensive and complete outpatient and home service for all illnesses for the workers and their families. The community hospitals already in existence would be used for hospitalization. If this plan did not work out, the labor unions would build and maintain their own hospitals. It is estimated that this complete service would be supplied for $4.50 a month for the worker alone, plus $6.00 for his family. These costs could be paid entirely by employers, or in some instances by employers and workers.

The San Francisco plan would be the first to be operated directly by a central labor council. Philadelphia has a medical center sponsored by the A. F. of L. Central Labor Union, but it is administered by the five or six unions whose 12,000 workers are served. Other labor health plans—notably those of the United Mine Workers, the Almagamated Garment Workers, the International Ladies' Garment Workers' Union, and the Teamsters' Union of St. Louis—are administered by the individual unions. The San Francisco experiment would be watched closely by unions eager to make more effective use of their health and welfare funds.

Inasmuch as A. F. of L. members and their families make up more than half of San Francisco's total population,* the new health plan would have a profound impact on the medical economy of the city. The American Medical Association sent staff members from its Chicago headquarters to report on the economic implications of the plan, and the San Francisco Medical Society created a special Labor Health Plan Study Committee to investigate the Labor Council's set-up. Its chairman, in a letter circulated to all local physicians, stated: "Union-labor health plans may bring drastic changes in the practice of medicine in the near future, and the profession must formulate plans to meet the challenge."

The San Francisco Medical Society Study Committee made an intensive investigation of this entire problem. On October 6, 1952, this committee made a report to the board of directors of the Medical Society based on a complete analysis of the Weinerman Report; a careful, detailed study of existing health centers in other parts of the United States (New York, Philadelphia, St. Louis); and extensive conferences with experts in the fields of economics, public health, and insurance. The membership of the Society was informed by editorials in the Bulletin of the San Francisco Medical Society and also by two general meetings of the membership, both so well attended that the auditorium was packed beyond capacity. In a questionnaire that was sent to 1,400 members of the Society, three questions were asked: 1. "Should the membership of the San Francisco Medical Society approve the proposed health centers under the A.F.L. formulated policy?" The result of this question showed that 26 members voted approval and 832 voted for Society disapproval of the health centers. Question 2: "Should the Medical Society formulate a plan of its own to be set up and approved by the Society under which services would be rendered to any and all prepaid medical plans which meet the approval of the Society?" The result showed 776 voting "Yes" and 79 "No." Question 3: "If such a plan is formulated, it will require adoption of a fee schedule to apply to income brackets below a certain income and subject to periodic revision. It must further be under the direct control of the membership of the San Francisco Medical Society. Would you approve a further effort to formulate a fee schedule to be presented to the members at a later date for their consideration?" There were 779 who voted approval, and 76 disapproval.

It was obvious to the members of the Study Committee that the membership wished the board of directors to set Society policy in disapproving the health centers. It was also obvious that the membership was ready to take a bold step forward in medical economic progress by proposing Society formulation and supervision of prepaid health and welfare

*From Dr. E. Richard Weinerman's report—San Francisco Labor Council Survey: Labor Plans for Health, 1952, June.

insurance, with a Society fee schedule to cover such plans. After this report was tendered to the board of directors, a new committee was formed to help draw up the fee schedule, to determine the criteria of medical care to be offered in Society-approved health insurance plans, and to set up a good public relations program which would help to explain to the public the part the physician plays in providing adequate medical care under the system of free choice of physician. This committee will also attempt to explain to the public the facts about the high costs of medical care today and to make clear the physician's position with regard to those costs.

At present the San Francisco Labor Council faces obstacles to its proposed plan of establishing the health centers. In the first place, the Medical Society voted overwhelmingly in disapproval of closed panel health centers with *complete union domination* and without free choice of physician. Another serious blow was that the Rockefeller Foundation turned down the Labor Council's request for a grant to enable it to start the project. The Labor Council seemed to feel that the Federal Government would provide subsidy for this program, but with the change in the national administration this year, this appears to be a remote possibility.

Spokesmen for the unions now have asked, in lieu of the health centers, that the Medical Society immediately set up a fee schedule for *union workers only* which would apply regardless of income.* They have also asked the Medical Society to help develop a plan of comprehensive coverage for all workers and dependents which could be bought for a moderate premium. These requests are now under consideration and it is the hope of the Medical Society that areas of agreement may soon be worked out. In the meantime, two of the smaller union groups have entered the Permanente Kaiser Foundation plan and several others have had to switch to modified benefit plans underwritten by commercial carriers. One large union has adopted a Blue Cross coverage providing limited home and office benefits and complete hospital and surgical coverage, and the union members and physicians appear at present to be satisfied with the plan. The contractors have provided hospitalization coverage alone for their employees. Permanente is making a concerted effort to enter the field of union health plans in San Francisco and Dr. Russel Lee of the Palo Alto Clinic has proposed a medical care plan comprising all the provisions of the Weinerman plan.

It has often been asked what would be the role of employers in the future development of the welfare plans. The Study Committee consulted with employers through the Employers Council of San Francisco. One of the leaders of the Council expressed the opinion that even should there be a depression and a lowering of wages, fringe benefits such as health and welfare insurance would still be paid for entirely by the employer. One big problem is that labor unions have sold their members on the idea of full medical coverage, including not only conservative and surgical treatment of patients in a physician's office, at home or in a hospital, but also a program of preventive medicine entailing full use of laboratory facilities in periodic examination of apparently well persons.

Since it is obvious that the aggregate cost of such a use of laboratory facilities would be great, it would seem wise for those interested in medical insurance of any kind to understand the potential financial burdens it would place on everyone involved. In insurance plans, the cost of caring for the sick is borne by the well. But if diagnostic facilities that usually are used only for the few persons who are sick come to be used quite as much for the examination of the many who are well, the basic principle of insurance does not apply: If all members of a plan receive benefits, the total cost of the plan increases and the premiums that pay that cost must be increased commensurately.

The constant demand for "comprehensive" care covering every minor and inexpensive illness that a person might have, tends to boost insurance rates and to take emphasis away from the much more necessary catastrophic coverage that would protect against serious chronic and disabling illness, which is the real robber of the working man's pocketbook. Such comprehensive insurance coverage has been declared to be prohibitive in cost by most of the recognized medical economists of the nation.

Members of the San Francisco Medical Society are interested in providing the best type of medical care for all the people in the community. They believe fervently that those who are dedicated to the care of the sick are best qualified to know what plans for medical care are best suited to various groups of persons. They are willing to formulate medically sponsored prepaid voluntary health insurance plans and to define and guarantee those criteria which will make these plans workable. Furthermore, they are willing to depart from the time-honored tradition of setting their own fees individually for services and to formulate an adequate fee schedule for the care of persons with annual income of $5,000 or less—the fee schedules to constitute a price list for medical services to persons in that income bracket.

*It should be noted that following extensive study by the committees involved and the Board of Directors of the San Francisco Medical Society, it was decided to try to formulate a fee schedule, but that it should be based on a yearly gross income of $5,000 or less, and apply to everyone in that income group, union member or not. Following this decision, representatives of all specialties worked together in the preparation of a proposed fee schedule. The schedule, together with its principles which are an integral part of it, was submitted to the active members of the society by mail ballot, on June 23, and the resulting vote was 799 to 173 in favor of its adoption. Since then society committees have been at work with representatives of insurance companies, Blue Cross, C.P.S., etc., considering ways and means of implementing the program.

Most physicians do not like fee schedules, for no two value their services alike, and it is difficult to standardize the value or price of personal services. Nevertheless, many specialty groups have worked successfully under fee schedules for years—for example, roentgenologists, medical laboratory specialists, pathologists, and industrial accident surgeons. These fees would have to provide for equitable compensation for specialists and general practitioners, and they should be subject to periodic revision.

Physicians must constantly be alert to the terrific impact on private practice of the proposals for labor-dominated closed panel health centers and any other utopian plan to provide medical service which does not guarantee free choice of physician and medical control of the plan. Too many physicians, busy with their own private practices, are not alert to the changing trends in the social and economic pattern, and cannot or will not concern themselves with the medical problems involved. They still seem to think that a medical society should be organized solely for scientific purposes and the medical education of its members, and should not consider and act upon the economic threats confronting the practice of medicine.

When persons begin to expect good health and sufficient medical facilities and personnel as a matter of course, they are deluded indeed. Good health is prevalent in our country only because countless physicians, dentists, nurses, teachers, and other citizens have struggled against the forces of disease, superstition and ignorance to create it. Anyone who is familiar with the many inferior medical educational institutions that existed in our country before 1910, and who knows of the long years of effort required to transform them into first-class schools capable of graduating large numbers of highly-trained physicians, is fully aware that an adequate number of skilled doctors cannot be expected as a matter of course. Such achievement is the result of hard work, and the American Medical Association has done its share. The doctrine that good things come to one as manna rather than through one's own efforts is the doctrine of dependence on an all-powerful welfare state, rather than belief in individual initiative and responsibility.

It is because of this that the union labor health and welfare problem in San Francisco has alerted our Medical Society to establish a new public relations study group, one of the important functions of which will be to call to the attention of the general public the contributions of their private physicians to the welfare of the country.

There is no doubt that union health plans are successful only when they follow clear-sighted medical direction. It is equally clear that unions are striving to work out medical service plans for their members. Therefore the medical profession has an opportunity to direct these plans into channels which are scientifically and medically advantageous, and such direction should be available if the time-honored standard of good medical practice is to be maintained.

The medical profession could modify the situation which fosters feelings of insecurity with regard to health in the industrial population. The difficulties workers experience in obtaining good medical care under the present methods of distribution create tension and foster political action.

Organized medicine could do more to have good concepts of better distribution accepted if it were to acquire thorough understanding of the health needs and security requirements of the organized industrial workers and take steps to help meet their needs. It is apparent that labor is convinced of the necessity of obtaining better access to good medical service and insurance protection during periods of illness. Action by the medical profession in devising satisfactory means to supply these demands would be far more effective in avoiding non-medical interference with medical practices than any official stand taken up to the present time.

2107 Van Ness Avenue.

THE PHYSICIAN'S *Bookshelf*

MONOGRAPHS IN MEDICINE—Series 1. Editor, William B. Bean, M.D., Professor and Head of the Department of Medicine, State University of Iowa. The Williams and Wilkins Company, Baltimore, 1952. 655 pages, $12.00.

The monographic method can be very helpful in bringing contemporary information to the doctor's desk. This is particularly true in fields where rapid advances have occurred in a very short time and where the average doctor is unable to keep pace with the accumulation of knowledge. The monograph provides a compromise between the monthly medical journal, which is focused on the temporal present, and the fully comprehensive volume which tries to cover the entire field of medical knowledge. The treatment is critical, and digested enough so that the average reader may recognize its utility and significance.

This first volume of a new series of collected monographs covers a wide variety of interests. The subjects have in common only that they summarize work about which there is a wide experimental interest or represent topics which have particular attraction for the editors. The monographs are of much the same type as those published in the quarterly journal *Medicine*. Among the subjects notably well done are those on the Physiology of Body Fluids, Portal Hypertension and Chemical Agents Used in the Treatment of Inoperable and Far-Advanced Neoplastic Diseases.

The reviewer believes there is a place for surveying "the scene from the medium hills, neither staying on the flats of day-by-day affairs nor climbing the high mountain for the grand and inclusive spectacle." He wonders if such attractively written but widely assorted material should not find its way into the magazine periodicals or the loose-leaf systems of medicine. However, since this venture is well begun it is hoped it will be long-lived.

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THE BASIS OF CLINICAL NEUROLOGY—The Anatomy and Physiology of the Nervous System in Their Application to Clinical Neurology—Third Edition. Samuel Brock, M.D., Professor of Neurology, College of Medicine, New York University. The Williams and Wilkins Company, Baltimore, 1953. 510 pages, $7.00.

This third edition of Brock's book is distinguished from its predecessors mainly by an increase in space devoted to description of the newer techniques in neurological diagnosis, notably, electroencephalography, electromyography and cerebral angiography. This reviewer has always been a little puzzled in how to classify this work; it cannot be considered a textbook of neuroanatomy, neurophysiology, nor yet clinical neurology, yet it treats of all these. It is probably more to be recommended to the serious student of neurology than to the medical student or the general practitioner of medicine, although it could be read with advantage by all. It is particularly instructive in giving a rather personalized evaluation of contemporary work in this now very wide field.

THE HISTORY OF AMERICAN EPIDEMIOLOGY. C.-E. A. Winslow, Dr.P.H., Professor Emeritus, Yale University School of Medicine; editor, American Journal of Public Health; Wilson G. Smillie, M.D., Professor and Chairman, Department of Public Health and Preventive Medicine, Cornell University Medical College; James A. Doull, M.D., Medical Director, Leonard Wood Memorial; John E. Gordon, M.D., Professor and Chairman, Department of Epidemiology, School of Public Health, Harvard University; edited by Franklin H. Top, M.D., Professor of Epidemiology and Pediatrics, College of Medical Sciences, University of Minnesota. Sponsored by The Epidemiology Section of the American Public Health Association. The C. V. Mosby Company, St. Louis, 1952. 190 pages, $4.75.

In times of rapid scientific and technological advancement, when the rush of new discoveries overwhelms assimilative capacities, it is easy to put aside historical books with the excuse that they have no immediate value and their truths will not decay. Yet it is at just such times that an occasional backward look has greatest value, helping us to relate our meandering course to the main line of development, restraining our enthusiasm for mere novelty and restoring our belief in the ultimate integration of things which at the moment seem hopelessly confused.

The History of American Epidemiology is a bold title, which might cover a book of broad scope, exhaustive in detail, and mainly concerned with the development of the intellectual discipline of epidemiology. Instead, it is the effort of four leading epidemiologists, well qualified by experience and expository skill to trace both the history of epidemic diseases in the United States and the broad outlines of epidemiological thinking in this country from colonial times to the present. Although brevity constrains the authors to merely list many significant events, the references to source materials are adequate for those who wish to go further into special topics. A large part is written in lucid narrative which can hardly fail to arouse wonderment at the tremendous advances in health conservation in the brief period of our national history, and interest in further study.

The most valuable contribution which the book offers to general medicine is a clear exposition of the concept of disease as the resultant of many forces, both internal and external. While most of us comprehend this in a general way, the more precise formulation which we can get from this book should enable us to serve our patients more fully and more efficiently. While not dwelt upon by these authors, the implications of this concept are broad, ramifying into such fields as the organization of medical insurance and group practice. The physician who thinks clearly along these lines will rarely be satisfied with superficial therapy of symptoms, or even the eradication of infection, except in the most trivial of illnesses.

Without burdening the reader with a complete review of medical history, this volume affords one of those brief backward glances which we need from time to time.

OFFICE PSYCHIATRY—The Management of the Emotionally and Mentally Disturbed Patient. Louis G. Moench, M.D., Assistant Clinical Professor of Medicine and of Psychiatry, University of Utah School of Medicine. The Year Book Publishers, Inc., 200 East Illinois Street, Chicago, 1952. 310 pages, $6.00.

Office Psychiatry by Dr. L. G. Moench, is an interesting book which deals with every phase of psychiatry from the psychosexual development of the child, problems in psychosomatic medicine and analysis to psychosurgery, all in 300 pages, and is limited as a result in explanation and clarity. It is a book of facts and near facts and due to the paucity of content, some of these are barely supported. Actually, little of the book pertains to the problems of office psychiatry; the book has almost nothing to contribute which would be helpful in managing patients.

Although it is quite obvious that the author, through his illustrations—and these are gems—has given evidence of his sympathy and of his understanding of the problems of mentally ill patients, he does not explain how to treat them, and one looks for this particularly in his chapter on "Psychotherapy."

Although many of his statements are factual, some sound dogmatic and rigid and many readers of the so-called "non-oriented" variety may take exceptions to his statements, particularly those found in the chapters on psychosomatic illnesses and their etiology. On the other hand, even psychiatrists of the so-called well oriented variety may feel justified in taking exception to such statements as are found in reference to treatment of choice in psychotics.

In short, the book is a quick look into the field of psychiatry and in reviewing the book, one recalls the quotation the author uses, "Brevity is best if it pursues the therapist rather than the therapist pursuing brevity."

The book should be excellent as one used for introducing psychiatry and its scope such as in introductory courses in schools, and perhaps, with a change in title, for laity.

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DANGER SIGNALS — Warnings of Serious Diseases. Walter C. Alvarez, M.D., Consultant in Medicine, Emeritus, Mayo Clinic. Wilcox & Follett Company, Chicago, 1953. 176 pages, $3.00.

Dr. Alvarez states that he is writing this book to save foolish worriers from needless anxiety and wise persons from avoidable illness and death. This is a lofty purpose. How practical it is in this case is open to question. Such a book must, inevitably, give a little knowledge to many people, and the old saw about a little knowledge being a dangerous thing is most true in the field of medicine. Dr. Alvarez's book is certain to send a number of its readers scurrying to their doctors, to arouse anxiety—without relief—in a number of others and to leave still others with a false sense of security.

The book is written in simple, fluent and highly personal style. It is organized in a logical manner, with a partial listing of the principal symptoms of many major and minor diseases. While it touches on a myriad of conditions, it digs deeply into none. It also dabbles in treatment and prognosis as well as diagnosis. All this makes for a very readable, if dangerously abbreviated, text of medicine.

Possibly the best chapter in the book is the last one—on how to choose a good doctor. While it does not cover all the ways, it does a reasonably satisfactory job.

The principal use of this book should be for the intelligent patient *with* a doctor, the patient who can analyze for himself *until* he gets medical care. This is the rare patient and, unfortunately, the book is far more likely to be seized upon by the apprehensive or the merely curious. The reviewer hopes, along with Dr. Alvarez, that it will relieve more anxiety than it causes—but he doubts it.

THE ESSENTIALS OF MEDICAL DIAGNOSIS—A Manual for Students and Practitioners. Rt. Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P. (Lond.), Extra Physician to H.M. the Queen; and A. E. Gow, M.D., F.R.C.P. (Lond.), Honorary Physician to Household, H.R.H. the Duchess of Kent. **Second Edition** Revised with the Assistance of Ronald Bodley Scott, M.A., D.M. (Oxon.), F.R.C.P. (Lond.), Physician to H.M. Household. The Williams and Wilkins Company, Baltimore, 1953. 462 pages, 6 color and 17 black and white plates, 22 figures and 5 charts, $6.00.

This book is remarkable in that the second edition appears some 25 years after the first. Despite this time lapse the main purpose of the book has not changed: it is to show the student how to start with a minimum of clues and, by the pursuit of proper methods, to construct a diagnosis. The authors have tried consistently to work from the patient and his complaint toward the disease from which he suffers, and not in the opposite direction. This system requires the observation of comparatively few salient signs, which must arouse in the observer the question for specific associated signs and symptoms.

The book attempts to cover the whole field of medical diagnosis in 428 pages. It contains considerable information, is well printed, and is liberally supplied with good illustrations. It is necessarily incomplete, mentioning many physical signs and mechanical aids in passing and leaving more adequate and detailed descriptions for other books.

It can be recommended only for students' reference or as a review text for the graduate with an examination to take. Incidentally, it demonstrates again that the method of teaching in English medical schools is different enough from that in ours so that, on the whole, English texts cannot substitute as primary teaching textbooks in American schools.

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PRINCIPLES AND PRACTICE OF MEDICINE—A Textbook for Students and Doctors. L. S. P. Davidson, B.A. Cantab., M.D., F.R.C.P.(Edin.), F.R.C.P.(Lond.), M.D.(Oslo), Physician to H.M. the Queen in Scotland, Professor of Medicine and Clinical Medicine, University of Edinburgh. The Williams and Wilkins Company, Baltimore, 1952. 919 pages, $6.75.

This new textbook of medicine is written entirely by the staff of the Department of Medicine of the University of Edinburgh. In effect, it represents the course in clinical medicine given at that medical school.

Each section of the book starts with a discussion of the anatomy and physiology of the systems concerned and ends with a review of the measures available for the prevention of disease. There is no orthodox chapter on the infectious diseases, although 28 pages are included in a general chapter entitled "Infection and Disease." There are no chapters devoted to pediatrics or psychiatry. There is no attempt to describe all of the rare diseases or syndromes. The chapter on tropical diseases is abbreviated.

The principal use of this book is for students of the University of Edinburgh and possibly other Scottish universities. It is too incomplete and regional to be used by American doctors or students.

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BEDSIDE DIAGNOSIS—2nd Edition. Charles Seward, M.D., F.R.C.P.(Edin.), Honorary Physician, Royal Devon and Exeter Hospitals; Consulting Physician, Princess Elizabeth Orthopedic Hospital. Williams and Wilkins Company, Baltimore, distributor for E. & S. Lvingstone, Ltd., London, 1952. 380 pages, $3.50.

The first edition of this book was reviewed in CALIFORNIA MEDICINE 73:208, August 1950.

There has not been sufficient change in the second edition to warrant another review.